

Access DB# 36303**SEARCH REQUEST FORM**

Scientific and Technical Information Center

Requester's Full Name: Pryor, Allen Examiner #: _____ Date: 10/26/04
Art Unit: 1616 Phone Number 30 _____ Serial Number: 10/049821
Mail Box and Bldg/Room Location: _____ Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: _____

Inventors (please provide full names): _____

Earliest Priority Filing Date: _____

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

Modified Search.

① lauroyl diethanolamide used to
treat mental/neurological disorders

② Structure ① Soap or shampoo.
a

STAFF USE ONLY

| | Type of Search | Vendors and cost where applicable |
|------------------------------------|-----------------------|-----------------------------------|
| Searcher: <u>Shapira</u> | NA Sequence (#) _____ | STN _____ |
| Searcher Phone #: _____ | AA Sequence (#) _____ | Dialog _____ |
| Searcher Location: _____ | Structure (#) _____ | Quest/Orbit _____ |
| Date Searcher Picked Up: _____ | Bibliographic _____ | Drink _____ |
| Date Completed: <u>10/27/04</u> | Litigation _____ | Lexis/Nexis <u>10/14/04</u> |
| Searcher Prep & Review Time: _____ | Fulltext _____ | Sequence Systems _____ |
| Clerical Prep Time: _____ | Patent Family _____ | WWW/Internet _____ |
| Online Time: _____ | Other _____ | Other (specify) _____ |

=> fil hcaplus
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FILE COVERS 1907 - 27 Oct 2004 VOL 141 ISS 18
 FILE LAST UPDATED: 26 Oct 2004 (20041026/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

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|----|--------|--|
| L3 | 2 | SEA FILE=REGISTRY ABB=ON PLU=ON ("LAURIC ACID DIETHANOLAMIDE"/CN OR "LAURIC ACID DIETHANOLAMIDE-MALEIC ANHYDRIDE-MYRISTIC ACID DIETHANOLAMIDE COPOLYMER"/CN) |
| L4 | 2 | SEA FILE=REGISTRY ABB=ON PLU=ON ("LAURIC DIETHANOLAMIDE"/CN OR "LAURIC DIETHANOLAMINE"/CN) |
| L5 | 3 | SEA FILE=REGISTRY ABB=ON PLU=ON L3 OR L4 |
| L6 | | SEL PLU=ON L5 1- CHEM : 103 TERMS |
| L7 | 7064 | SEA FILE=HCAPLUS ABB=ON PLU=ON L6 |
| L8 | 88622 | SEA FILE=HCAPLUS ABB=ON PLU=ON ("NERVOUS SYSTEM, DISEASE"/CV OR "DISEASE, ANIMAL"/CV OR "DISEASES, BY BODY PART (NON-CA HEADING)/CV OR "ORGAN, ANIMAL, DISEASE"/CV OR "BRAIN, DISEASE"/CV OR "MENTAL DISORDER"/CV OR "MENTAL DISORDER (L) DEMENTIA"/CV OR "DEMENTIA"/CV OR "DEMENTIA MENTAL DISORDER"/CV) |
| L9 | 107784 | SEA FILE=HCAPLUS ABB=ON PLU=ON "NERVOUS SYSTEM, DISEASE"/CV OR "BRAIN, DISEASE"/CV OR "MENTAL DISORDERS"/CV OR "PSYCHIATRY/CV OR "ALZHEIMER'S DISEASE"/CV OR "AMNESIA/CV OR "BRAIN, DISEASE (L) MULTI-INFARCT DEMENTIA"/CV OR "HYSTERIA/CV OR "INSOMNIA/CV OR "MENKES' SYNDROME"/CV OR "MENTAL RETARDATION"/CV OR "AMAUROTIC FAMILIAL IDIOCY"/CV OR "AMAUROTIC FAMILIAL IDIOCY (L) CEROID LIPOFUSCINOSIS, NEURONAL"/CV OR "CHROMOSOME (L) HUMAN X, DISEASE, FRAGILE"/CV OR "COCKAYNE'S SYNDROME"/CV OR "DOWN'S SYNDROME"/CV OR "FRAGILE X SYNDROME"/CV OR "GANGLIOSI DOSIS/CV OR "AMAUROTIC FAMILIAL IDIOCY (L) INFANTILE"/CV OR "SANDHOFF'S DISEASE"/CV OR "LESCH-NYHAN SYNDROME"/CV OR "MENTAL DISORDER (L) RETARDATION, X-LINKED"/CV OR "MENTAL DISORDER (L) RETARDATION, CLASPED THUMB AND MENTAL RETARDATION"/CV OR "MENTAL DISORDER (L) RETARDATION, WITH PROGRESSIVE EPILEPSY"/CV OR "MONGOLISM/CV OR "NEIMANN-PICK DISEASE"/CV OR "NEURONAL CEROID LIPOFUSCINOSIS"/CV OR "AMAUROTIC FAMILIAL IDIOCY (L) CEROID LIPOFUSCINOSIS, NEURONAL, INFANTILE"/CV OR "AMAUROTIC FAMILIAL IDIOCY (L) INFANTILE NEURONAL CEROID LIPOFUSCINOSIS"/CV OR "AMAUROTIC FAMILIAL IDIOCY (L) JUVENILE"/CV OR "NIEMANN-PICK DISEASE"/CV OR "PHENYLKETONURIA/CV OR "PRADER-WILLI SYNDROME"/CV OR "SCHIZOPHRENIA/CV OR "CATATONIA/CV |

OR "ELECTROCONVULSIVE THERAPY"/CV OR "HYPNOTICS AND SEDATIVES"/
 CV OR "MENTAL ACTIVITY"/CV OR "NERVOUS SYSTEM DEPRESSANTS"/CV
 OR "NEUROTRANSMITTER AGONISTS"/CV OR "NEUROTRANSMITTER
 ANTAGONISTS"/CV OR PSYCHOTROPICS/CV OR "THERAPY (L) PSYCHOTHERA
 PY"/CV OR TRANQUILIZERS/CV OR "CATECHOL METHYLTRANSFERASE"/CV
 OR "ISOBUTYL IODIDE"/CV)

L10 146287 SEA FILE=HCAPLUS ABB=ON PLU=ON L8 OR L9
 L11 69417 SEA FILE=HCAPLUS ABB=ON PLU=ON ("NERVOUS SYSTEM, DISEASE"/CV
 OR "MOVEMENT DISORDERS"/CV OR "PARKINSON'S DISEASE"/CV OR
 PARKINSONISM/CV OR "LEWY BODY DISEASE"/CV OR "RAMSAY HUNT
 PARALYSIS SYNDROME"/CV OR "PARKINSONISM (L) GUAMANIAN PARKINSON
 ISM-DEMENTIA"/CV OR "PARKINSONISM (L) HEMI"/CV OR "ANTIPARKINSON
 IAN AGENTS"/CV OR TREMOR/CV OR A-SYNUCLEIN/CV OR
 "1,2,3,6-TETRAHYDRO-1-METHYL-4-PHENYLPYRIDINE"/CV OR 1-METHYL-4
 -PHENYLPYRIDINIUM/CV OR 6-HYDROXYDOPAMINE/CV OR DOPAMINE/CV)

L12 197499 SEA FILE=HCAPLUS ABB=ON PLU=ON L10 OR L11
 L14 43444 SEA FILE=HCAPLUS ABB=ON PLU=ON ("AGING, ANIMAL"/CV OR
 "AGING, ANIMAL (L) SENILITY"/CV OR "SENESCENCE (L) SENILITY"/CV
 OR "SENESCENCE AND SENILITY"/CV OR SENILITY/CV)

L15 236064 SEA FILE=HCAPLUS ABB=ON PLU=ON L12 OR L14
 L16 28543 SEA FILE=HCAPLUS ABB=ON PLU=ON (EMOTION/CV OR ANXIETY/CV OR
 ANXIETIES/CV OR MOOD/CV OR ANXIOLYTICS/CV OR "NERVOUS SYSTEM
 DEPRESSANTS"/CV OR "STRESS, ANIMAL"/CV)

L17 256779 SEA FILE=HCAPLUS ABB=ON PLU=ON L15 OR L16
 L18 35017 SEA FILE=HCAPLUS ABB=ON PLU=ON ("STRESS, BIOLOGICAL"/CV OR
 "STRESS, ANIMAL"/CV OR "STRESS, ANIMAL (L) JET LAG"/CV OR "JET
 LAG"/CV OR "JET LAG SYNDROME"/CV)

L19 273569 SEA FILE=HCAPLUS ABB=ON PLU=ON L17 OR L18
 L23 27 SEA FILE=HCAPLUS ABB=ON PLU=ON L7(L) (JET(W)LAG OR ?MELANCO?
 OR ?DEPRESS? OR ?SENIL? OR ?DEMENTI? OR ?INSOM? OR ?PARKIN? OR
 ?ALZHE? OR ?ANXIET?)

L25 2 SEA FILE=HCAPLUS ABB=ON PLU=ON L7(L)L19
 L27 29 SEA FILE=HCAPLUS ABB=ON PLU=ON L23 OR L25

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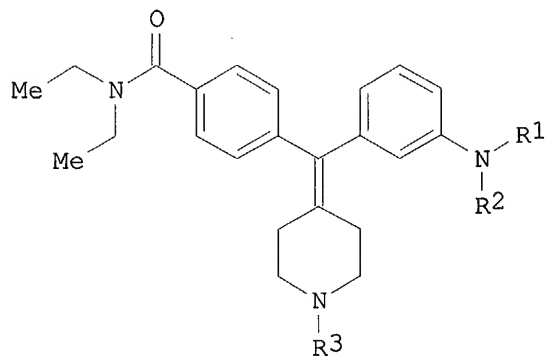
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L27 ANSWER 1 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2004:412920 HCAPLUS
 DOCUMENT NUMBER: 140:423590
 TITLE: Preparation of 4-(phenylpiperidin-4-
 ylidenemethyl)benzamides for treatment of pain,
 anxiety, or gastrointestinal disorders
 INVENTOR(S): Brown, William; Griffin, Andrew
 PATENT ASSIGNEE(S): Astrazeneca AB, Swed.
 SOURCE: PCT Int. Appl., 96 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

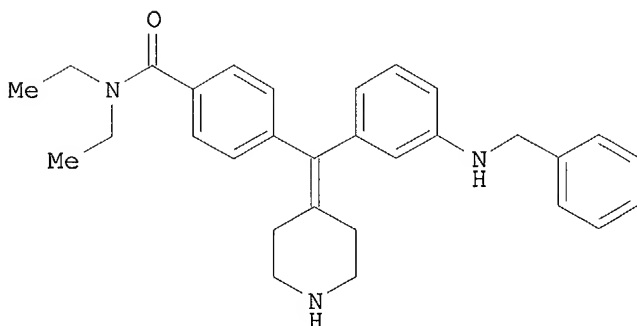
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------|---|----------|-----------------|----------|
| WO 2004041784 | A1 | 20040521 | WO 2003-SE1705 | 20031105 |
| W: | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, | | | |

TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ,
 BY, KG, KZ, MD
 RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE,
 BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU,
 MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN,
 GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: SE 2002-3301 A 20021107
 OTHER SOURCE(S): MARPAT 140:423590
 GI



I



II

AB Title compds. I [wherein R1 = (un)substituted alkyl, cycloalkyl(alkyl), (hetero)aryl, R8CO, R8SO2, R8SO, R8NHCO, R8CS, or R8NHCS; ; R2 = H or (un)substituted alkyl; R3 = H or (un)substituted alkoxy carbonyl, alkyl, or cycloalkyl(alkyl); R8 = (un)substituted alkyl, (hetero)aryl(alkyl), or cycloalkyl(alkyl); or pharmaceutically acceptable salts thereof] were prepared as opioid δ receptor ligands. For example, reaction of 4-(bromomethyl)benzoic acid Me ester with P(OMe)₃, followed by addition of 1-(tert-butoxycarbonyl)-4-piperidone in the presence of **LDA** in THF, gave 4-(4-methoxycarbonylbenzylidene)piperidine-1-carboxylic acid tert-Bu ester (35%). Addition of Br₂ (78%) and reaction with NaOH in MeOH provided 4-[bromo(4-carboxyphenyl)methylene]piperidine-1-carboxylic acid tert-Bu ester (87%). Conversion to the benzoyl chloride with iso-Bu chloroformate and amidation (73%) with Et₂NH in the presence of TEA in CH₂Cl₂, followed by coupling with 3-aminophenylboronic acid using Pd(PPh₃)₄ and Na₂CO₃ in toluene/EtOH/H₂O afforded N,N-diethyl-4-[(3-aminophenyl)(piperidin-4-ylidene)methyl]benzamide (97%). Alkylation of the amine with benzaldehyde and NaBH(OAc)₃ in 1,2-dichloroethane gave II. In binding assays using human 293S cells expressing cloned human opioid receptors and neomycin resistance, most compds. of the invention exhibited activity toward the δ receptor with IC₅₀ values in the range of 0.14

nM - 31.2 nM. Exemplified compds. also showed some activity toward the κ and μ receptors with IC50 values in the ranges of 36 nM - 9680 nM and 3 nM - 5975 nM, resp. Thus, I and their pharmaceutical compns. are useful in therapy, in particular for the treatment of gastrointestinal disorders, **anxiety**, or pain (no data).

L27 ANSWER 2 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:719487 HCAPLUS

DOCUMENT NUMBER: 139:246044

TITLE: Bicyclic pyridine and pyrimidine derivatives, e.g., thieno[2,3-d]pyrimidines and analogs, active as p38 kinase inhibitors, and their preparation, pharmaceutical compositions, and uses

INVENTOR(S): Chen, Jian Jeffrey; Dewdney, Nolan James; Stahl, Christoph Martin

PATENT ASSIGNEE(S): F. Hoffman-La Roche Ag, Switz.

SOURCE: PCT Int. Appl., 80 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|--|----------|-----------------|------------|
| WO 2003074530 | A1 | 20030912 | WO 2003-EP2090 | 20030228 |
| W: | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | |
| RW: | GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | |
| US 2003207900 | A1 | 20031106 | US 2003-383392 | 20030306 |
| PRIORITY APPLN. INFO.: | | | US 2002-362373P | P 20020307 |
| | | | US 2002-430508P | P 20021203 |
| OTHER SOURCE(S): | MARPAT 139:246044 | | | |
| GI | | | | |

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention discloses compds. I, their pharmaceutical formulations, methods of making them, and their uses in the treatment of p38 kinase-mediated diseases [wherein: A is N or CH; R1 is H, alkyl or arylalkyl; R2 is alkyl, hydroxyalkyl, (R'')2NCO-alkylene- (where each R'' is independently H or alkyl), cycloalkyl, heterocyclyl, aryl, heteroaryl, or heteroalkyl; X is O, NR3, or S, wherein R3 is H, alkyl, or aryl; and Y is bond, O, NR', CO, CH(OR'), CH(R'), or S(O)n, wherein n = 0-2; and R' is H or alkyl; and R is aryl or heteroaryl; or an isomer, a pharmaceutically acceptable salt, an ester, or a prodrug thereof]. The compds. are useful for treatment of disorders exacerbated or caused by excessive or unregulated TNF or p38 kinase production. Claimed methods of treatment include uses for treatment of arthritis, Crohn's disease, **Alzheimer's** disease, irritable bowel syndrome, adult respiratory distress syndrome, and chronic obstructive pulmonary disease. A table of over 40 compds. I is given, and most of these compds. are also claimed individually. The example compds. are mostly thienopyrimidines, but include some

furanopyrimidines and pyrrolopyrimidines. For instance, invention compound II (as the HCl salt) was prepared from 4-chloro-2-(methylthio)pyrimidine in 5 steps: (1) fluorination of chloro using KF and 18-crown-6 in tetraglyme; (2) lithiation in the 5-position with LDA and formylation with EtOCHO; (3) cyclocondensation of the resultant aldehyde with 2'-ClC₆H₄COCH₂SH to form a fused thiophene ring; (4) oxidation of the methylthio group to a Me sulfone using Oxone; and (5) aminolysis of the sulfone with 4-aminotetrahydropyran, followed by chromatog. and acidification in ether. In a test for inhibition of recombinant p38 kinase in vitro, invention compound III gave an IC₅₀ of 104 nM.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 3 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:511075 HCAPLUS

DOCUMENT NUMBER: 139:85242

TITLE: Preparation of 2-oxindole derivs. as glycogen synthase kinase-3 (GSK3) inhibitors for use in pharmaceutical compositions for treatment of neurodegenerative diseases

INVENTOR(S): Berg, Stefan; Bhat, Ratan; Empfield, James; Hellberg, Sven; Klimas, Michael; Woods, James

PATENT ASSIGNEE(S): Astrazeneca Ab, Swed.

SOURCE: PCT Int. Appl., 36 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

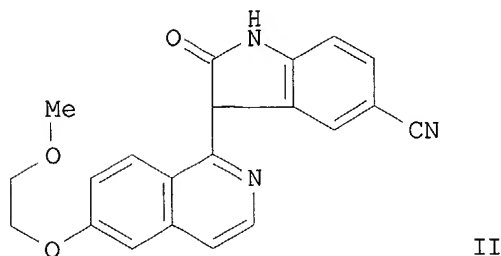
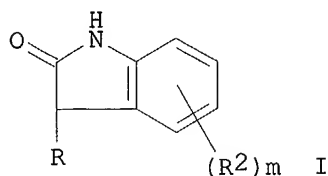
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|--|----------|-----------------|------------|
| WO 2003053330 | A2 | 20030703 | WO 2002-SE2373 | 20021218 |
| WO 2003053330 | A3 | 20031030 | | |
| W: | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | |
| RW: | GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | |
| EP 1458707 | A2 | 20040922 | EP 2002-793678 | 20021218 |
| R: | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK | | | |
| PRIORITY APPLN. INFO.: | | | SE 2001-4340 | A 20011220 |
| | | | WO 2002-SE2373 | W 20021218 |

OTHER SOURCE(S): MARPAT 139:85242

GI



AB 2-Oxindoles, such as I [R = substituted or unsubstituted nitrogen containing heteroaryl, such as 2-isoquinyl, thieno[2,3-b]pyrimidin-4-yl or 5,6,7,8-tetrahydroquinazolin-4-yl; R₂ = OH, CH₂F, CF₃, OCF₃, CN, NH₂, NO₂, alkyl, alkoxy, acyloxy, acyl, alkylthio, etc.; m = 0-4], were prepared for therapeutic use as GSK3 inhibitors. These oxindoles are intended for therapeutic use in the treatment of GSK3 associated diseases, such as **Alzheimer's disease, dementia, Parkinson's disease, dementia complex of Guam, frontotemporal dementia, Parkinson's type, HIV dementia, neurofibrillar tangle pathologies, predemented states, vascular dementia, dementia with Lewy bodies, dementia pugilistic and age related cognitive disorders, as well as for male contraception and treatment of diabetes, amyotrophic lateral sclerosis, corticobasal degeneration, Down's syndrome, Huntington's disease, Parkinson's disease, postencephalatic Parkinsonism, progressive supranuclear palsy, Pick's disease, Niemann-Pick's disease, stroke, head trauma, bipolar disease, affective disorders, depression, schizophrenia, cognitive disorders and androgenetic alopecia.** Thus, oxindole II was prepared in 51% yield by a coupling reaction of 5-cyanooxindole with 1-chloro-6-(2-methoxyethoxy)isoquinoline using **LDA** and TMEDA in anhydrous THF under a N₂ atmospheric. The prepared oxindoles were tested for GSK3 inhibition using the GSK3β proximity assay.

L27 ANSWER 4 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:319690 HCAPLUS

DOCUMENT NUMBER: 138:309341

TITLE: Percutaneous absorption preparations for the treatment of dementia

INVENTOR(S): Terahara, Takaaki; Toshimitsu, Arata; Uemura, Kengo; Higo, Naruhito; Goto, Takeshi; Sato, Shuji

PATENT ASSIGNEE(S): Hisamitsu Pharmaceutical Co., Inc., Japan

SOURCE: PCT Int. Appl., 30 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------|--|----------|-----------------|----------|
| WO 2003032960 | A1 | 20030424 | WO 2002-JP10785 | 20021017 |
| W: | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | |
| RW: | GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, | | | |

CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
 EP 1437130 A1 20040714 EP 2002-777864 20021017
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
 IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK
 PRIORITY APPLN. INFO.: JP 2001-319510 A 20011017
 WO 2002-JP10785 W 20021017

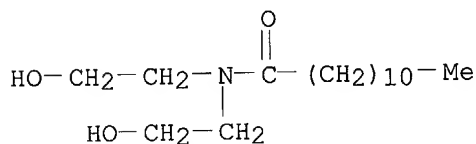
AB Disclosed are percutaneous absorption preps. for treating dementia which contain an adhesive composition, characterized in that the adhesive composition contains the active ingredient in a dispersed state. The active ingredient, acetylcholine esterase inhibitor, is released at a pharmacol. effective speed and the skin permeation speed thereof is at least 1.2 µg/cm²/h. Thus, it is possible to provide percutaneous absorption preps. whereby the therapeutic effect can be sustained over a prolonged period of time without elevating the concentration of the active ingredient in the plasma to such a level as causing the expression of side effects in the administration of remedies for dementia. A transdermal tape was formulated containing styrene-isoprene-styrene block copolymer 17.1, polyisobutylene 7.3, Arkon P100 41.6, paraffin oils 29.4, NaOAc 0.6, donepezil hydrochloride 1, and pirotiodecane 3 %.

IT **120-40-1, Lauric acid diethanolamide**

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (percutaneous absorption preps. containing acetylcholine esterase inhibitors in adhesives for treatment of **dementia**)

RN 120-40-1 HCAPLUS

CN Dodecanamide, N,N-bis(2-hydroxyethyl)- (6CI, 8CI, 9CI) (CA INDEX NAME)



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 5 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:133023 HCAPLUS

DOCUMENT NUMBER: 138:169963

TITLE: Synthesis of sulfonamido-substituted bridged bicycloalkyl derivatives for control of beta-amyloid production

INVENTOR(S): Hannam, Joanne Claire; Harrison, Timothy; Madin, Andrew; Sparey, Timothy Jason

PATENT ASSIGNEE(S): Merck Sharp & Dohme Limited, UK

SOURCE: PCT Int. Appl., 67 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------|--|----------|-----------------|----------|
| WO 2003013506 | A1 | 20030220 | WO 2002-GB3559 | 20020731 |
| W: | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | |
| RW: | GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, | | | |

CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
NE, SN, TD, TG

US 2004186147 A1 20040923 US 2004-484290 20040120
PRIORITY APPLN. INFO.: GB 2001-19152 A 20010806
WO 2002-GB3559 W 20020731

OTHER SOURCE(S): MARPAT 138:169963
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. I [A,B = together with the carbon atoms bonded to L1R4 and H complete a (un)substituted ring containing 5-10 carbon atoms; R1 = H, alkyl, alkenyl; R2 = H, acyl; R3 = alkyl, cycloalkyl, alkenyl, alkynyl, aryl, etc.; R4 = H, halo, aryl, heterocyclyl, CN, alkoxy, amino, etc.; L1 = bond, alkylene, etc.] are prepared For instance, Et cyclopentanone-2-carboxylate was reacted with o-xylylene dibromide (DMF, NaOEt) and the resulting adduct treated with LDA in THF at -78° to give
II. II was treated in the following manner: i. THF, H2NOH•HCl, NaOAc; ii. HOAc, H2-PtO; iii. CH2Cl3, Et3N, 5-chlorothiophenesulfonyl chloride and iv. THF, LAH to provide sulfonamide III. I modulate the production of β-amyloid from amyloid precursor protein and are useful in the treatment of **Alzheimer's** disease.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 6 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:5924 HCAPLUS

DOCUMENT NUMBER: 138:73016

TITLE: Improved process for preparation of cyclohexanol derivatives, e.g., 1-[cyano(4-methoxyphenyl)methyl]cyclohexanol, a venlafaxine intermediate, from phenylacetone nitriles and cyclohexanone, using non-organometallic bases.

INVENTOR(S): Kim, Keun-sik; Kim, Kwang-il; Lee, Sung-woo; Park, Jin-soo; Chai, Ki-byung

PATENT ASSIGNEE(S): Wyeth A Corporation of the State of Delaware, USA, USA
SOURCE: PCT Int. Appl., 23 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

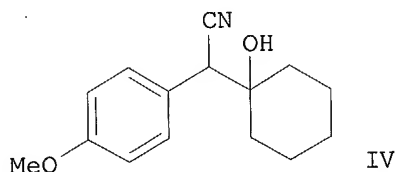
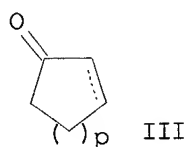
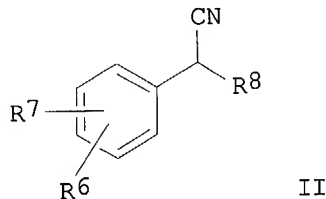
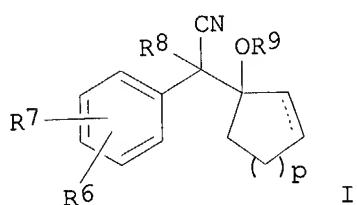
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------|--|----------|-----------------|----------|
| WO 2003000652 | A1 | 20030103 | WO 2002-US19753 | 20020621 |
| WO 2003000652 | C1 | 20040521 | | |
| W: | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | |
| RW: | GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | |
| EP 1397344 | A1 | 20040317 | EP 2002-744526 | 20020621 |
| R: | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, | | | |

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|--|----|-----------------|
| IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | |
| BR 2002010542 | A | 20040622 |
| JP 2004531577 | T2 | 20041014 |
| US 2004186310 | A1 | 20040923 |
| PRIORITY APPLN. INFO.: | | |
| | | BR 2002-10542 |
| | | JP 2003-507059 |
| | | US 2003-481679 |
| | | KR 2001-35889 |
| | | KR 2001-10 |
| | | WO 2002-US19753 |
| | | A 20010622 |
| | | A 20010622 |
| | | W 20020621 |

OTHER SOURCE(S): CASREACT 138:73016; MARPAT 138:73016
GI



AB An improved process for the preparation of cyanobenzylated cyclohexanol derivs. and analogs I is claimed [wherein: R6 and R7 are ortho or para substituents, independently selected from the group consisting of H, OH, C1-C6 alkyl, C1-C6 alkoxy, C7-C9 aralkoxy, C2-C7 alkanoyloxy, C1-C6 alkylmercapto (sic), halo, or CF₃; R8 is H or C1-C6 alkyl; p is 0, 1, 2, 3 or 4; and R9 is H or C1-C6 alkyl]. Reaction of phenylacetone nitriles II with cycloalk(an/en)ones III in the presence of a non-organometallic base catalyst IV or V, in the presence or absence of a reaction solvent, gives I [wherein: A is (CH₂)_n where n is 2 to 4; B is (CH₂)_m where m is 2 to 5; X is CH₂, O, NH or NR', where R' is C1-C4 alkyl or acyl, or an alkyl supporting polymer; and each of R1 to R4 is independently H, alkyl, cycloalkyl, or an alkyl or cycloalkyl supporting polymer, and all of R1 to R4 are not H; R5 is alkyl, cycloalkyl, or an alkyl or cycloalkyl supporting polymer; and where R9 is an alkyl, the alkyl group is introduced by alkylation]. The products, such as IV, are useful intermediates for **antidepressants** such as venlafaxine. Known methods relying upon organometallic bases such as n-BuLi are expensive, at risk of fire or explosion, give low yields, and are impractical on an industrial scale. In contrast, the invention method is simple, economical, scalable to industrial production, safe, and environmentally friendly. Only small, catalytic amts. of the base are needed, and use of organic solvents is avoided. Both yields and purity of products are high. For instance, solventless reaction of 0.68 mol p-methoxyphenylacetone nitrile with 1.02 mol cyclohexanone in the presence of 0.21 mol DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) for 48 h at 15-20°, followed by addition of 1N HCl to acid pH and stirring for 1 h at room temperature, gave IV in 84% yield by simple precipitation and filtration, m. 123.7°. The same procedure with only 0.1 equiv DBU and a reaction time of 6 days gave 90.5% yield. In contrast, a standard, more complex preparation of using n-BuLi in THF gave only 34.2% yield of lower-purity IV. Another preparation using **LDA** (from n-BuLi and diisopropylamine) gave 79% yield of IV, but required a large amount of toluene as solvent.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 7 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:839647 HCAPLUS
 DOCUMENT NUMBER: 138:301103
 TITLE: Contrasting phenotypes of C57BL/6J01aHsd, 129S2/SvHsd and 129/SvEv mice in two exploration-based tests of anxiety-related behaviour
 AUTHOR(S): Rodgers, R. J.; Boullier, E.; Chatzimichalaki, P.; Cooper, G. D.; Shorten, A.
 CORPORATE SOURCE: Behavioural Pharmacology Laboratory, University of Leeds, School of Psychology, Leeds, LS2 9JT, UK
 SOURCE: Physiology & Behavior (2002), 77(2-3), 301-310
 CODEN: PHBHA4; ISSN: 0031-9384
 PUBLISHER: Elsevier Science Inc.
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Knockout mice are typically generated on a mixed genetic background and, as such, detailed behavioral characterization of these background strains is essential to the valid interpretation of mutant phenotypes. In this context, recent research has revealed significant differences in **anxiety**-like behavior among the most commonly used background strains (C57BL/6J and various 129 substrains), leading to the possibility that at least certain mutant phenotypes may not after all be due to the targeted mutation. However, these findings derive largely from behavioral test batteries in which there may well be an experiential confound, while the widely reported hypolocomotor profile of most 129 substrains may compromise the principal indexes of **anxiety**-like behavior. In the present study, we have compared the behavioral profiles of three commonly used background strains (C57BL/6J01aHsd, 129/SvEv and 129S2/SvHsd) in two of the most popular animal models of **anxiety** -the elevated plus-maze (EPM) and light/dark exploration (**LDE**) tests. Naive animals were used for each procedure, ethol. scoring methods were employed throughout, and the inbred phenotypes were also compared with that of an outbred strain (Swiss-Webster) widely employed in test validation and behavioral pharmacol. Our results show that, despite their hypolocomotor profile, both 129 substrains display higher levels of **anxiety**-like behavior (conventional and/or ethol. measures) relative to the C57BL/6J01aHsd strain. Furthermore, all three inbred strains were less active in both tests when compared with the outbred Swiss-Webster strain. However, whereas C57BL/6J01aHsd mice displayed lower levels of **anxiety**-like behavior than their Swiss-Webster counterparts (both tests), 129S2/SvHsd (but not 129/SvEv) mice exhibited evidence of higher **anxiety**, particularly in the **LDE** test. The implications of these findings are discussed in relation to both the behavioral and pharmacol. phenotyping of mutant mice.
 REFERENCE COUNT: 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 8 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2001:896639 HCAPLUS
 DOCUMENT NUMBER: 137:72898
 TITLE: Long-term administration of Amlodipine prevents decompensation to diastolic heart failure in hypertensive rats
 AUTHOR(S): Nishikawa, Nagahiro; Masuyama, Tohru; Yamamoto, Kazuhiro; Sakata, Yasushi; Mano, Toshiaki; Miwa, Takeshi; Sugawara, Motoaki; Hori, Masatsugu
 CORPORATE SOURCE: Department of Internal Medicine and Therapeutics, Osaka University, Suita, Japan
 SOURCE: Journal of the American College of Cardiology (2001), 38(5), 1539-1545
 CODEN: JACCDI; ISSN: 0735-1097

PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Objectives: The authors assessed the effects of long-term Amlodipine administration in a diastolic heart failure (DHF) rat model with preserved systolic function as well as the relationship between changes in left ventricular (LV) myocardial stiffening and alterations in extracellular matrix. Background: Although the effect of long-term administration of Amlodipine has been shown to be disappointing in patients with systolic failure, the effect is unknown in those with DHF. Methods: Dahl salt-sensitive rats fed a high-salt diet for 7 wk were divided into 3 groups: 8 untreated rats (DHF group), 8 rats given high-dose Amlodipine (10 mg/kg/day; HDA group), and 7 rats given low-dose Amlodipine (1 mg/kg/day; LDA group). Results: High-dose administration of Amlodipine decreased systolic blood pressure and controlled excessive hypertrophy, without a decrease in the collagen content, and prevented the elevation of LV end-diastolic pressure at 19 wk. Low-dose administration of Amlodipine with **subdepressive** effects did not control either hypertrophy or fibrosis; however, it prevented myocardial stiffening and, hence, the elevation of LV end-diastolic pressure. The ratio of type I to type III collagen mRNA levels was significantly lower in both the HDA and LDA groups than in the DHF group. Conclusions: Long-term administration of Amlodipine prevented the transition to DHF both at the **depressor** and **subdepressor** doses. Amlodipine did not decrease the collagen content, but attenuated myocardial stiffness, with inhibition of the phenotype shift from type III to type I collagen. Thus, Amlodipine may exert beneficial effects through amelioration of collagen remodeling in the treatment of DHF.

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

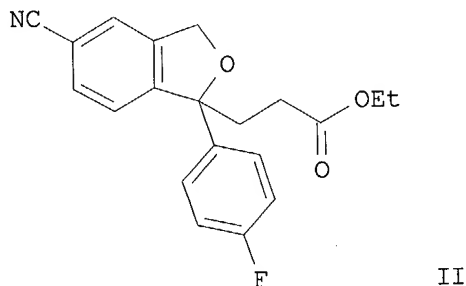
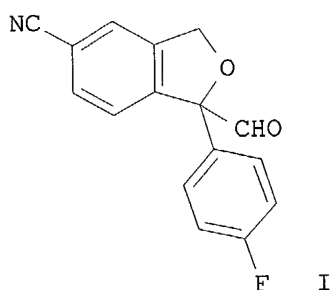
L27 ANSWER 9 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:693303 HCAPLUS
DOCUMENT NUMBER: 135:257140
TITLE: Stepwise alkylation of 5-substituted
1-(4-fluorophenyl)-1,3-dihydroisobenzofurans
(citalopram intermediates)
INVENTOR(S): Petersen, Hans; Ahmadian, Haleh
PATENT ASSIGNEE(S): H. Lundbeck A/S, Den.
SOURCE: PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------|--|----------|-------------------|----------|
| WO 2001068629 | A1 | 20010920 | WO 2001-DK159 | 20010309 |
| W: | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | |
| RW: | GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | |
| EP 1265881 | A1 | 20021218 | EP 2001-913735 | 20010309 |
| R: | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | |
| TR 200202195 | T2 | 20021223 | TR 2002-200202195 | 20010309 |

| | | | | |
|------------------------|----|----------|----------------|------------|
| BR 2001009364 | A | 20021224 | BR 2001-9364 | 20010309 |
| JP 2003527385 | T2 | 20030916 | JP 2001-567721 | 20010309 |
| NZ 521204 | A | 20040326 | NZ 2001-521204 | 20010309 |
| BG 107046 | A | 20030530 | BG 2002-107046 | 20020902 |
| ZA 2002007024 | A | 20030902 | ZA 2002-7024 | 20020902 |
| US 2003083509 | A1 | 20030501 | US 2002-242804 | 20020910 |
| NO 2002004352 | A | 20021008 | NO 2002-4352 | 20020912 |
| PRIORITY APPLN. INFO.: | | | DK 2000-403 | A 20000313 |
| | | | DK 2000-414 | A 20000314 |
| | | | WO 2001-DK159 | W 20010309 |

OTHER SOURCE(S):
GI

CASREACT 135:257140; MARPAT 135:257140

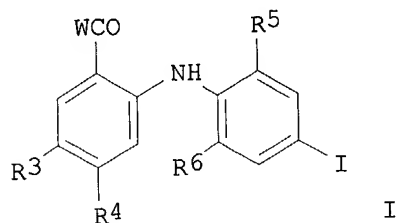


AB Methods for manufacture of citalopram, well-known **antidepressant**, through stepwise alkylation of 5-R-substituted 1-(4-fluorophenyl)-1,3-dihydroisobenzofurans [R = CN, OH, NH₂, etc.] are disclosed. Thus, reacting 1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile with Me formate in the presence of **LDA** in THF followed by reacting the resulting 1-formyl intermediate I with tri-Et phosphonoacetate in the presence of **LDA** in THF, hydrogenation of the crude intermediate, and reacting the intermediate II with Me chloroaluminum dimethylamide in PhMe afforded citalopram.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 10 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2001:142150 HCAPLUS
 DOCUMENT NUMBER: 134:193213
 TITLE: Preparation of carboxydiarylamine for pharmaceuticals
 INVENTOR(S): Tecle, Haile
 PATENT ASSIGNEE(S): Warner Lambert Co., USA
 SOURCE: Jpn. Kokai Tokkyo Koho, 68 pp.
 CODEN: JKXXAF
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|------|-------------------|-----------------|------------|
| JP 2001055376 | A2 | 20010227 | JP 1999-53567 | 19990302 |
| PRIORITY APPLN. INFO.: | | | US 1999-115650P | P 19990113 |
| OTHER SOURCE(S): | | MARPAT 134:193213 | | |
| GI | | | | |



AB Title compds. I (W = ORB, NR2OR1, NRARB, NR2NRARB, O(CH2)nNRARB, NR2(CH2)mNRARB; n = 2-4; m = 1-4; R1, RA, RB = H, C1-8 alkyl, C3-8 alkenyl, C3-8 alkynyl, C3-8 cycloalkyl; R2 = H, C1-4 alkyl, Ph, C3-6 cycloalkyl; one of R3 and R4 = H, F, the other = C2-6 heterocyclyl, C3-7 cycloalkyl, C2-6 heterocyclyl C1-4 alkyl; R5 = H, Me, Cl; R6 = H, F). The compds. are useful for treatment of psoriasis, restenosis, autoimmune disease, atherosclerosis, cancers, heart failure, symptoms of xenograft rejection, osteoarthritis, rheumatoid arthritis, asthma, cystic fibrosis, hepatomegaly, cardiomegaly, Alzheimer's disease, diabetes, septic shock, and HIV. 2-Fluoro-4-aminobenzoic acid was cyclized with 2,5-dimethoxytetrahydrofuran in the presence of NaOAc in AcOH under reflux for 3 h 76% 2-fluoro-4-(pyrrol-1-yl)benzoic acid, which was condensed with 2-methylfluoroaniline in the presence of LDA in THF at room temperature for 16 h to give 93% I (W = OH, R3, R6 = H, R4 = pyrrol-1-yl, R5 = Me).

L27 ANSWER 11 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2001:51658 HCAPLUS

DOCUMENT NUMBER: 135:165946

TITLE: Inhibition of the allograft response by donor specific blood transfusion: Association with reduced local TH1 cytokines and nitric oxide but enhanced prostaglandin E2 production

AUTHOR(S): Koga, Shigehiko; Luke, Patrick P.; Specht, Susan M.; Rominski, Barbara; Jaquins-Gerstl, Andrea; Hoffman, Rosemary A.; Thomson, Angus W.; Jordan, Mark L.

CORPORATE SOURCE: Departments of Urology and Surgery, University of Pittsburgh Medical Center and Veterans Administration Medical Center, Pittsburgh, PA, 15213, USA

SOURCE: Transplantation (2000), 70(12), 1788-1796
CODEN: TRPLAU; ISSN: 0041-1337

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Donor-specific blood transfusion (DST) may improve allograft survival in human and animal models, but the mechanisms for this graft protective effect are incompletely understood. The sponge matrix allograft model was used to determine if DST induces regulatory factors within the allograft. C57BL/6 (H-2b) recipients received donor-specific (DBA/2J, H-2d) or syngeneic (C57BL/6) blood 7 days before sponge matrix allograft (DBA/2J) implantation. Fourteen days postgrafting, the sponge infiltrating cells (SIC) were examined for cytotoxic T cell (CTL) and natural killer (NK) activity, and sponge exudate fluid (SEF) was assessed for nitric oxide (N=O) and prostaglandin E2 (PGE2) content. Interleukin- (IL) 2, IL-4, IL-10, and interferon- γ (IFN- γ) production by SIC was also determined. Recipient splenocytes were simultaneously assessed for anti-donor cytotoxic and proliferative responses and N=O production. SIC from mice receiving syngeneic transfusions (ST) acquired both CTL and NK activity postgrafting, with maximal activity by day 14. DST suppressed both CTL and NK activity throughout the postgrafting period. Limiting dilution anal. (LDA) of SIC to determine precursor and native CTL

frequency showed significantly lower responder cell frequency after DST compared with ST. SEF ·N=0 levels and SIC production of IL-2 and IFN- γ in grafted DST mice were significantly lower than in grafted mice receiving ST. No significant amts. of IL-4 and very low levels of IL-10 were produced by SIC from grafted mice after either ST or DST. Conversely, PGE2 content of sponge fluid and serum from DST mice was higher than in mice receiving ST. Antigen stimulated splenocyte proliferation and CTL development assessed by LDA were also inhibited by DST. Reduction in local TH1 cytokines, absence of detectable TH2 cytokines, with enhanced PGE2 and depressed ·N=0 were observed in the local graft environment after DST. These data support the hypothesis that DST induces donor-specific intragraft suppressor factors, accompanied by reduced local and systemic immune activation.

REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 12 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2000:493533 HCAPLUS

DOCUMENT NUMBER: 133:105039

TITLE: Preparation of heterocyclyl diphenylamines as MEK inhibitors

INVENTOR(S): Tecle, Haile; Barrett, Stephen Douglas; Bridges, Alexander James; Zhang, Lu-Yan

PATENT ASSIGNEE(S): Warner-Lambert Company, USA

SOURCE: PCT Int. Appl., 95 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

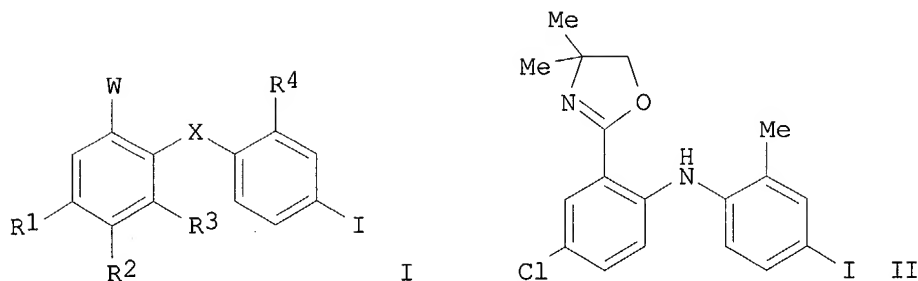
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-------------------|-------------|
| WO 2000042029 | A1 | 20000720 | WO 1999-US30416 | 19991221 |
| W: AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| JP 2000204077 | A2 | 20000725 | JP 1999-53564 | 19990302 |
| CA 2355374 | AA | 20000720 | CA 1999-2355374 | 19991221 |
| EP 1144394 | A1 | 20011017 | EP 1999-968150 | 19991221 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| BR 9916896 | A | 20011120 | BR 1999-16896 | 19991221 |
| TR 200102029 | T2 | 20011121 | TR 2001-200102029 | 19991221 |
| JP 2002534515 | T2 | 20021015 | JP 2000-593597 | 19991221 |
| EE 200100374 | A | 20021216 | EE 2001-374 | 19991221 |
| NZ 513432 | A | 20040227 | NZ 1999-513432 | 19991221 |
| ZA 2001005219 | A | 20020925 | ZA 2001-5219 | 20010625 |
| NO 2001003451 | A | 20010712 | NO 2001-3451 | 20010712 |
| HR 2001000525 | A1 | 20030630 | HR 2001-525 | 20010712 |
| BG 105801 | A | 20020731 | BG 2001-105801 | 20010809 |
| US 6545030 | B1 | 20030408 | US 2002-889104 | 20020117 |
| US 2003004193 | A1 | 20030102 | US 2002-201146 | 20020723 |
| PRIORITY APPLN. INFO.: | | | US 1999-115875P | P 19990113 |
| | | | US 1999-122420P | P 19990302 |
| | | | WO 1999-US30416 | W 19991221 |
| | | | US 2002-889104 | A3 20020117 |

OTHER SOURCE(S): MARPAT 133:105039
GI



AB The title compds. (I) [wherein W = (un)substituted N-containing 5-membered ring; X = O, S, NH, or N(alkyl); R1 and R2 = independently H, F, NO₂, Br, or Cl; or R1 = SO₂NRGRH; or R1 and R2 together with the benzene ring to which they are attached = indole, isoindole, benzofuran, benzothiophene, indazole, benzimidazole, or benzthioazole; R3 = H or F; R4, RG, and RH = independently H, Cl, or Me] were prepared for treating MEK mediated conditions (no data). For example, 5-chloro-2-methoxybenzoic acid was converted to the acid chloride using SOCl₂ and 2-amino-2-methyl-1-propanol added to give the 4,4-dimethyl-4,5-dihydrooxazol-2-yl intermediate (77%). The oxazole was then added to a solution of **LDA** and 4-iodo-2-methylaniline in THF to yield the diphenylamine II (81%). I are useful in the treatment of proliferative disease, such as psoriasis, restenosis, autoimmune disease, and atherosclerosis, cancer, stroke, heart failure, xenograft rejection, osteoarthritis, rheumatoid arthritis, cystic fibrosis, hepatomegaly, cardiomegaly, **Alzheimer's** disease, diabetes, septic shock, and viral infection, including HIV infection (no data). For treating cancer, I may be administered in conjunction with a mitotic inhibitor, such as paclitaxel, docetaxel, vincristine, vinblastine, vinorelbine, or vinflunine (no data).

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 13 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1999:519556 HCAPLUS

DOCUMENT NUMBER: 131:144610

TITLE: Methods of preparing substituted 3-phenyl- and 3-pyridyl-4(3H)-quinazolinones and atropisomers thereof, useful as AMPA inhibitors or their intermediates

INVENTOR(S): Chenard, Bertrand Leo; Shenk, Kevin Dale

PATENT ASSIGNEE(S): Pfizer Products Inc., USA

SOURCE: Eur. Pat. Appl., 31 pp.

CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

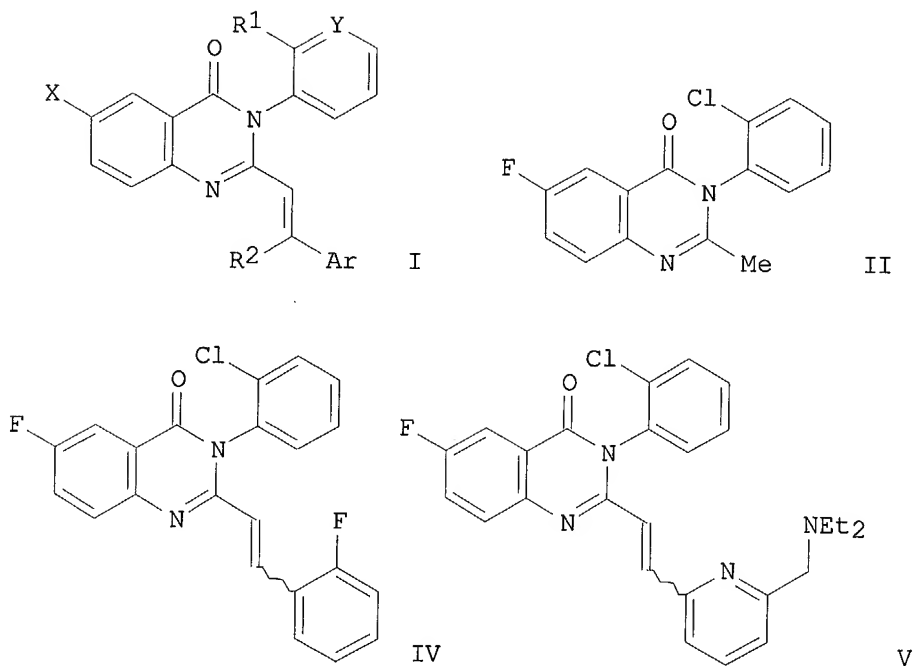
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|------------|
| EP 934934 | A2 | 19990811 | EP 1999-300839 | 19990204 |
| EP 934934 | A3 | 19991013 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| JP 11279158 | A2 | 19991012 | JP 1999-24901 | 19990202 |
| CA 2260701 | AA | 19990809 | CA 1999-2260701 | 19990205 |
| BR 9901996 | A | 20000502 | BR 1999-1996 | 19990209 |
| PRIORITY APPLN. INFO.: | | | US 1998-74150P | P 19980209 |

OTHER SOURCE(S):
GI

CASREACT 131:144610; MARPAT 131:144610



AB The invention is directed to (1) methods for preparation of quinazolin-4-one derivs. I and their atropisomers and/or pharmaceutically acceptable salts, and (2) atropisomeric intermediates II and their enantiomers [wherein R¹ = halo, cyano, alkyl, perfluoroalkyl, alkoxycarbonyl; R² = H or OH; X = H, OH, halo, CF₃, NO₂, (un)substituted alkyl, alkoxy, acyl, etc.; Y = N or CH; Ar = (un)substituted Ph or various 5- or 6-membered heteroarom. rings]. I are α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) inhibitors (no data), and are useful for the treatment of various neurol. disorders and conditions including **Parkinson's Disease**, epilepsy, emesis, ischemia, stroke, traumatic brain and spinal cord injury, etc. Preps. include preps. of 8 compds. I, 2 of which are atropisomeric salts, as well as 3 racemic intermediates, and 4 atropisomeric intermediates II. For instance, 3-(2-chlorophenyl)-6-fluoro-2-methyl-3H-quinazolin-4-one, i.e., (\pm)-II [R¹ = Cl, X = F, Y = CH; (\pm)-III] was deprotonated with **LDA** and treated with 2-fluorobenzaldehyde to give a diastereomeric mixture of alcs. (38%), which was dehydrated by (CF₃CO)₂O in dioxane to give 57% title compound IV. Alternatively, (\pm)-III was resolved by chromatog. on Chiralcel AD[®], and the obtained (+)-III was similarly converted to title compound (+)-V (as the 1.5 mesylate salt).

L27 ANSWER 14 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1999:282452 HCAPLUS

DOCUMENT NUMBER: 131:102122

TITLE: Synthetic studies of epolactaene, a novel γ -lactam natural product

AUTHOR(S): Shiraki, R.; Shiraga, Y.; Tadano, K.

CORPORATE SOURCE: Department of Applied Chemistry, Keio University, Japan

SOURCE: Tennen Yuki Kagobutsu Toronkai Koen Yoshishu (1997),

39th, 415-420
 CODEN: TYKYDS
 PUBLISHER: Nippon Kagakkai
 DOCUMENT TYPE: Journal
 LANGUAGE: Japanese
 GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB In recent years, some highly C- and O-substituted chiral γ -lactams possessing a variety of biol. activities were isolated from microorganisms. Epolactaene was isolated from the culture broth of *Penicillium* sp. BM 1689-P by Osada et al. in 1995. This natural product shows the novel neuritogenic activities in a human neuroblastoma cell line, SH-SY5Y cells. Therefore, epolactaene was expected to be pharmaceutically potent on various neurodegenerative diseases including **dementia**. The planer structure of epolactaene, containing an unsatd. twelve-carbon acyl side chain at the α -position of the γ -lactam ring, both hydroxy and Me groups at the γ -position, and an epoxy ring at α,β -position, was determined by spectroscopic anal. (^1H - and ^{13}C -NMR). However, the stereochem. of the epoxy moiety remained to be determined. The authors have recently completed the first total synthesis of PI-091 from D-glucose-derived branched sugar derivative I. The authors planned to synthesize epolactaene and present here their synthetic approach to epolactaene from I, the starting material of the total synthesis of PI-091. The authors' synthetic strategy involves the following three key reactions: (1) an aldol reaction of an acyclic ketone II prepared from I with the lithium enolate of acetone providing a diastereomeric mixture of adducts III [$R = Q$], (2) transformation of III [$R = Q$] into a 2,4-substituted furan IV, and (3) photochem. addition of singlet oxygen to the silylated furan III [$R = Q1$] to construct the desired γ -lactone III [$R = Q2$]. First, II was prepared via Wittig olefination of aldehyde derived from I followed by some functional group transformations in eight steps. The aldol reaction of II with acetone smoothly proceeded by using **LDA** as a base to give III [$R = Q$] as a diastereomeric mixture. In further synthetic venture, an important intermediate γ -hydroxy- γ -lactone III [$R = Q2$] was obtained via the photosensitized singlet oxygen addition of α -silylfuran III [$R = Q1$], which was derived from III [$R = Q$] via deprotection of the pivalate, acid treatment, followed by α -silylation of the resulting furan. The authors next pursued construction of the triene part of the side chain in epolactaene. For the purpose of a stepwise carbon elongation, III [$R = Q2$] was first converted into V via Wittig olefination. The second step of carbon elongation of V and total synthesis of epolactaene are now in progress.

L27 ANSWER 15 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 1999:144449 HCAPLUS
 TITLE: The alkylation and reduction of O-TBS substituted indanone oximes
 AUTHOR(S): Figueroa, Dylana; Ortiz-Marciales, Margarita; Lopez, Jose; De Jesus, Melvin
 CORPORATE SOURCE: Department of Chemistry, University of Puerto Rico, Humacao, 00791, P. R.
 SOURCE: Book of Abstracts, 217th ACS National Meeting, Anaheim, Calif., March 21-25 (1999), CHED-172. American Chemical Society: Washington, D. C. CODEN: 67GHA6
 DOCUMENT TYPE: Conference; Meeting Abstract
 LANGUAGE: English

AB Aminoindanes are important compds. with a variety of physiol. activity, such as bronchodilator agents and blood pressure **depressants**. We have synthesized O-TBS substituted indanone oximes as precursors for the synthesis of several primary amino derivs. by the reduction of the C=N bond. The azaenolate of O-TBS oxime of 1-indanone was generated by the addition of **LDA** at -78 C, which was subsequent quenched with Et bromide, as electrophile, obtaining a 60% yield of corresponding pure 2-Et O-silylated oxime. Results for the reduction of the alkylated substituted oximes with borane-THF complex to obtain the 1-aminoindanes will be discussed. Further studies for the synthesis of 2-aminoindane derivs. are in progress.

L27 ANSWER 16 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1999:48698 HCAPLUS

DOCUMENT NUMBER: 130:124900

TITLE: Preparation of 4-bromo or 4-iodo phenylamino benzhydroxamic acid derivatives as MEK inhibitors

INVENTOR(S): Barrett, Stephen Douglas; Bridges, Alexander James; Doherty, Annette Marian; Dudley, David Thomas; Saltiel, Alan Robert; Tecle, Haile

PATENT ASSIGNEE(S): Warner-Lambert Company, USA

SOURCE: PCT Int. Appl., 65 pp.

CODEN: PIXXD2

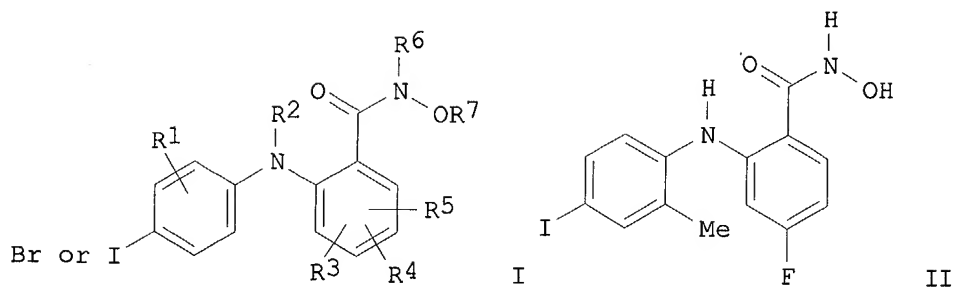
DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|-------------------|----------|------------------|-------------|
| WO 9901426 | A1 | 19990114 | WO 1998-US13106 | 19980624 |
| W: AL, AU, BA, BB, BG, BR, CA, CN, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| AU 9882627 | A1 | 19990125 | AU 1998-82627 | 19980624 |
| AU 757046 | B2 | 20030130 | | |
| EP 993439 | A1 | 20000419 | EP 1998-932830 | 19980624 |
| EP 993439 | B1 | 20040929 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| BR 9810366 | A | 20000829 | BR 1998-10366 | 19980624 |
| NZ 501276 | A | 20001027 | NZ 1998-501276 | 19980624 |
| JP 2002511092 | T2 | 20020409 | JP 1999-507228 | 19980624 |
| TW 396149 | B | 20000701 | TW 1998-87110252 | 19980625 |
| ZA 9805728 | A | 19990127 | ZA 1998-5728 | 19980630 |
| MX 9910649 | A | 20000430 | MX 1999-10649 | 19991118 |
| NO 9906491 | A | 19991229 | NO 1999-6491 | 19991227 |
| US 2003078428 | A1 | 20030424 | US 2002-163890 | 20020604 |
| PRIORITY APPLN. INFO.: | | | US 1997-51440P | P 19970701 |
| | | | WO 1998-US13106 | W 19980624 |
| | | | US 2000-462239 | B1 20000104 |
| OTHER SOURCE(S): | MARPAT 130:124900 | | | |
| GI | | | | |



AB The title compds. [I; R1 = H, OH, C1-8 alkyl, etc.; R2 = H; R3-R5 = H, OH, halo, etc.; R6 = H, C1-8 alkyl, aryl, etc.; R7 = H, C1-8 alkyl, C2-8 alkenyl, etc.], which are potent inhibitors of MEK and, as such, are effective in treating cancer and other proliferative diseases such as psoriasis, restenosis, autoimmune disease, or atherosclerosis, and also stroke, heart failure, hepatomegaly, cardiomegaly, diabetes, **Alzheimer's** disease, and cystic fibrosis, were prepared and formulated. Thus, treatment of 2-amino-5-iodotoluene in THF with **LDA** in THF/heptane/ethylbenzene solution followed by addition of 2,4-difluorobenzoic acid in THF, and reaction of the resulting 4-fluoro-2-(4-iodo-2-methylphenylamino)benzoic acid with O-(tetrahydro-2H-pyran-2-yl)hydroxylamine in the presence of diisopropylethylamine and PyBOP in THF/CH₂Cl₂, and treatment of the intermediate with ethanolic HCl afforded II which showed IC₅₀ of 0.007 μ M against MEK in vitro.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 17 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 1997:433181 HCAPLUS
 DOCUMENT NUMBER: 127:55927
 TITLE: Flurazepam patches with good bioavailability
 INVENTOR(S): Hashimoto, Michiari; Yoneto, Kunio
 PATENT ASSIGNEE(S): Sekisui Chemical Co. Ltd., Japan
 SOURCE: Jpn. Kokai Tokkyo Koho, 4 pp.
 CODEN: JKXXAF
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|------|----------|-----------------|----------|
| JP 09136835 | A2 | 19970527 | JP 1995-295307 | 19951114 |
| PRIORITY APPLN. INFO.: | | | JP 1995-295307 | 19951114 |

AB The title patches comprise a support and an overcoating adhesive layer containing (A) pressure-sensitive adhesive copolymers of 50-80 mol% C2-18 alkyl (meth)acrylates and 20-50 mol% vinylpyrrolidone (I), (B) flurazepam 1-20, (C) iso-Pr myristate (II) 10-40, (D) lauric acid diethanolamide (III) 1-15, and (E) SiO₂ as irritation-reducing agents 5-20 weight% (based on the total adhesive layer). A patch containing 2-ethylhexyl acrylate-1,6-hexamethylene glycol dimethacrylate-I copolymer 90.0, flurazepam 10.0, II 30.0, III 10.0, and Aerosil 200 (SiO₂) 17.0 parts (by weight) was applied to isolated murine skin to show flurazepam permeation 262 μ g/cm².

L27 ANSWER 18 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 1997:433180 HCAPLUS
 DOCUMENT NUMBER: 127:55926

TITLE: Ibudilast patches with good bioavailability
 INVENTOR(S): Hashimoto, Michiari; Yoneto, Kunio
 PATENT ASSIGNEE(S): Sekisui Chemical Co. Ltd., Japan
 SOURCE: Jpn. Kokai Tokkyo Koho, 4 pp.
 CODEN: JKXXAF
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|------|----------|-----------------|----------|
| JP 09136834 | A2 | 19970527 | JP 1995-295308 | 19951114 |
| PRIORITY APPLN. INFO.: | | | JP 1995-295308 | 19951114 |

AB The title patches comprise a support and an overcoating adhesive layer containing (A) pressure-sensitive adhesive copolymers of 10-60 weight% C₆ alkyl (meth)acrylates and 40-90 weight% 2-ethylhexyl methacrylate (I), (B) ibudilast 1-20, (C) iso-Pr myristate (II) 10-40, (D) lauric acid diethanolamide (III) 0.1-5, and (E) SiO₂ as irritation-reducing agents 5-20 weight% (based on the total adhesive layer). A patch containing dodecyl methacrylate-2-ethylhexyl acrylate-I-1,6-hexamethylene glycol dimethacrylate copolymer 50.5, ibudilast 8.8, II 26.5, III 2.7, and Aerosil 200 (SiO₂) 11.5 weight% was applied to guinea pigs to show good bioavailability.

L27 ANSWER 19 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 1997:148223 HCAPLUS
 DOCUMENT NUMBER: 126:176688
 TITLE: Effervescent bath tablets with good strength and fast dissolution
 INVENTOR(S): Takahashi, Naryuki; Tanaka, Norihiro; Suzuki, Junko; Yorozu, Hidenori
 PATENT ASSIGNEE(S): Kao Corp, Japan
 SOURCE: Jpn. Kokai Tokkyo Koho, 5 pp.
 CODEN: JKXXAF
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

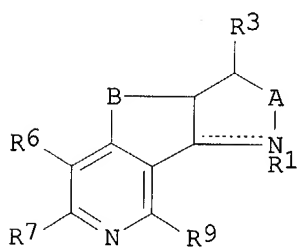
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|------|----------|-----------------|----------|
| JP 09002942 | A2 | 19970107 | JP 1995-154191 | 19950621 |
| JP 3555908 | B2 | 20040818 | | |
| PRIORITY APPLN. INFO.: | | | JP 1995-154191 | 19950621 |

AB The bath tablets contain (a) solid containing $\geq 10\%$ surfactants and carbonate salts at ≥ 2 times the atmospheric of the surfactants, (b) carbonate salts or hydrogen carbonate salts, and (c) organic acids at the content of (a) 3-20 weight%. The tablets may have **depression** on the center. A bath tablet prepared from a mixture containing polyoxyethylene lauryl ether 1.0, **lauric acid diethanolamide** 0.5, K₂CO₃ 4.5 (the above components were premixed under heating), Na₂CO₃ 5, NaHCO₃ 23.5, glucose 20, fumaric acid 40, PEG 6000 5, and perfume 0.5 weight% showed strength 9.5 kg and dissoln. time in bath water (40°) 10.16 min, vs. 4.5 kg and 16.05 min, resp., for a control tablet containing dextrin instead of K₂CO₃.

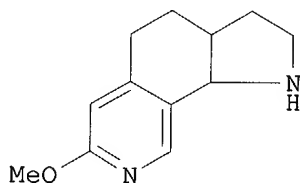
L27 ANSWER 20 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 1996:455773 HCAPLUS
 DOCUMENT NUMBER: 125:114581
 TITLE: Polycyclic fused-ring modulators of acetylcholine receptors
 INVENTOR(S): Whitten, Jeffrey P.; Mcdonald, Ian A.; Vernier,

PATENT ASSIGNEE(S): Jean-Michel
 Slak Institute Biotechnology/Industrial Associates,
 Inc., USA
 SOURCE: PCT Int. Appl., 58 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|-------------------|----------|-----------------|----------|
| WO 9611931 | A1 | 19960425 | WO 1995-US12905 | 19950928 |
| W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM | | | | |
| RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| US 5567710 | A | 19961022 | US 1994-322757 | 19941013 |
| AU 9538280 | A1 | 19960506 | AU 1995-38280 | 19950928 |
| PRIORITY APPLN. INFO.: | | | US 1994-322757 | 19941013 |
| | | | WO 1995-US12905 | 19950928 |
| OTHER SOURCE(S): | MARPAT 125:114581 | | | |
| GI | | | | |



I



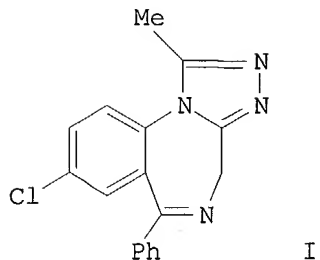
II

AB The invention provides a class of polycyclic fused-ring compds. I [A, B = 1- to 3-atom bridging groups; R1 = H, alkyl, (un)substituted aryl or alkaryl, or R1 is absent if optional double bond is present; R3, R9 = H, alkyl; R6, R7 = H, (un)substituted alkyl, alkenyl, alkynyl, aryl, aralkyl, aroyl, or heteroaryl, acyl, halo, CF₃, cyano, NO₂, etc.; with some exclusions], which are modulators of acetylcholine receptors (no data). I displace acetylcholine receptor ligands from their binding sites, and may act as agonists, partial agonists, antagonists or allosteric modulators. I are thus potentially useful for treatment of a variety of CNS disorders, in particular **Parkinson's** and **Alzheimer's** disease and other **dementias**, and as analgesics. For example, Michael-type reaction of 3-methoxy-8-oxo-5,6,7,8-tetrahydroisoquinoline with nitroethylene, using **LDA** and ZnCl₂ in THF at -78° to -60°, gave 89% 7-(2-nitroethyl) derivative. Reduction of this over Raney Ni gave 82% cyclic imine, which was further reduced with NaBH₃CN in MeOH to give 59% title compound II. In addition to displacing ligands such as quinuclidinyl benzilate and methylcarbamylocholine at micromolar concns., I prevented haloperidol-induced catalepsy in rats (34% reduction at 3 mg/kg, s.c.), and gave 52% of maximum activity orally in the tail-flick analgesia assay in rats, with a duration of action 3 times as long as morphine.

L27 ANSWER 21 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 1994:182710 HCAPLUS
 DOCUMENT NUMBER: 120:182710
 TITLE: Acadesine improves surgical myocardial protection with blood cardioplegia in ischemically injured canine hearts
 AUTHOR(S): Vinten-Johansen, J.; Nakanishi, Katsuhiko; Zhao, Zhi Qing; McGee, D. Scott; Tan, Ping
 CORPORATE SOURCE: Dep. Cardiothorac. Surg., Bowman Gray Sch. Med., Winston-Salem, NC, 27157-1096, USA
 SOURCE: Circulation (1993), 88(5, Pt. 2), 350-8
 CODEN: CIRCAZ; ISSN: 0009-7322
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB Adenosine is a cardioprotective autacoid that exerts receptor-mediated protection from ischemia/reperfusion injury. In ischemia-injured hearts, avoidance of ischemia/reperfusion injury with hypothermic chemical cardioplegia may be incomplete, and consequently, postischemic left ventricular (LV) function may be severely **depressed** and chamber stiffness increased. This study tested the hypothesis that the adenosine-regulating agent acadesine improves myocardial protection with hypothermic blood cardioplegia (BCP), resulting in better postischemic LV function and diastolic characteristics in hearts injured by 45 min of normothermic global ischemia. Eighteen anesthetized (350 µg fentanyl citrate, 5 mg diazepam) dogs on total vented bypass were randomized to receive vehicle, low-dose acadesine (**LDA**, 0.125 mg/kg/min) or high-dose acadesine (**HDA**, 0.5 mg/kg/min) continuously infused 30 min before global ischemia and discontinued 10 min after aortic cross-clamp removal. Hearts were protected with cold (4°) multidose (every 20 min) potassium BCP, which contained saline vehicle, 1 mg/L acadesine (**LDA**), or 4 mg/L acadesine (**HDA**) for a total of 1 h of cardioplegic arrest. Postischemic LV function, assessed by the slope of the end-systolic pressure-volume (impedance catheter) relation, was **depressed** by 34% of baseline (5.6 vs. 2.7 mm Hg/mL) in vehicle. With **LDA**, there was variable improvement in postischemic function (5.1 vs. 3.6 mm Hg/mL, vs. baseline). In contrast, there was complete postischemic functional recovery with **HDA** (5.9 vs. 5.2 mm Hg/mL). Postischemic chamber stiffness was preserved in both **LDA** and **HDA**. The authors conclude that the higher dose of acadesine improves myocardial protection when used as a pretreatment and BCP adjuvant, resulting in better postischemic LV systolic function and diastolic characteristics.

L27 ANSWER 22 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 1993:87506 HCAPLUS
 DOCUMENT NUMBER: 118:87506
 TITLE: Enhancement effects in the permeation of Alprazolam through hairless mouse skin
 AUTHOR(S): Carelli, V.; Di Colo, G.; Nannipieri, E.; Serafini, M. F.
 CORPORATE SOURCE: Inst. Pharm. Chem., Univ. Pisa, Pisa, Italy
 SOURCE: International Journal of Pharmaceutics (1992), 88(1-3), 89-97
 CODEN: IJPHDE; ISSN: 0378-5173
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 GI



AB Alprazolam (I) is an anxiolytic, **antidepressant** agent, having suitable features for the development of a transdermal medication. The objectives of this preliminary study were to determine: (a) whether I is absorbed in vitro through hairless mouse skin; (b) whether it is metabolized during diffusion, and (c) the influence of some chems. on I penetration through skin. I permeates through hairless mouse skin in vitro. No degradation product of the drug resulted during skin permeation expts., therefore, I was assumed to diffuse unchanged across the skin. Oleic acid (OLA), linoleic acid (LNA), linoleic acid diethanolamide (LNDA), coconut fatty acid diethanolamide (CNDA), **lauric acid diethanolamide (LRDA)**, bis(2-hydroxyethyl)cocamine (HECA) and iso-Pr lanolate (IPL) were evaluated with respect to their skin-permeation enhancing effect either as neat solvents or combined with propylene glycol (PG). All the vehicles excepting IPL and PG were more effective than OLA in enhancing transdermal absorption of I. The most effective was HECA followed by LNDA, CNDA and LNA/PG (8.5:1.5, weight/weight). The effects of skin pretreatment with HECA, LNA, LNDA and CNDA on the percutaneous absorption of I was greater than that from IPL or OLA through untreated skin. In order to facilitate the interpretation of the absorption results, the stratum corneum/water, whole skin/water and n-octanol/water partition coeffs. of the drug were determined

L27 ANSWER 23 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1992:414571 HCAPLUS
 DOCUMENT NUMBER: 117:14571
 TITLE: Schottky barriers at epitaxial silicide/silicon interfaces
 AUTHOR(S): Fujitani, Hideaki; Asano, Setsuro
 CORPORATE SOURCE: Fujitsu Lab. Ltd., Atsugi, 243-01, Japan
 SOURCE: Applied Surface Science (1992), 56-58(Pt. A, Proc. Int. Conf. Form. Semicond. Interfaces, 3rd, 1991), 408-15
 CODEN: ASUSEE; ISSN: 0169-4332
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB The electronic structure was studied of the YSi₂/Si(111) and NiSi₂/Si(001) interfaces using the linear muffin-tin orbitals in the atomic sphere approximation (LMTO-ASA) based on the local d. approximation (**LDA**). Together with the previous results on the CoSi₂/Si(111) and NiSi₂/Si(111) interfaces, LMTO-ASA calcns. with a large supercell give an adequate Schottky barrier height (SBH: EF - EV) for real silicide/Si interfaces although the **LDA depresses** the band gap of bulk Si to almost half of the exptl. value. An eightfold NiSi₂/Si(001) interface showed almost the same SBH as the type A NiSi₂/Si(111) interface. From the relation between the interface structure and the calculated SBH, the bond angle at the interface affects the SBH.

L27 ANSWER 24 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1991:597988 HCAPLUS
 DOCUMENT NUMBER: 115:197988

TITLE: Analysis of retinoid-mediated immunosuppression in vivo. Effects of Ro23-6457 on cellular alloimmune responses

AUTHOR(S): Orosz, Charles G.; Zinn, Nancy E.; Bishop, D. Keith; Leppink, Douglas L.; Faherty, Denise; Ferguson, Ronald M.

CORPORATE SOURCE: Coll. Med., Ohio State Univ., Columbus, OH, 43210, USA

SOURCE: Immunopharmacology (1991), 22(1), 49-58

CODEN: IMMUDP; ISSN: 0162-3109

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The authors investigated the immunosuppressive effects of a synthetic retinoid, Ro23-6457, on the in vivo development of cellular alloimmunity. They initially observed that treatment of C57B1/6 mice with 10 mg/kg/day Ro23-6457 drug could prolong the survival of DBA/2 cardiac allografts, thus verifying its immunosuppressive potential in murine exptl. methods. They next used the sponge matrix model of allograft rejection and limiting dilution anal. (**LDA**) of cytotoxic T lymphocyte (CTL) frequency to dissect this phenomenon further. In this exptl. system they observed the following effects of Ro23-6457: (1) dose-dependent decrease in the number of **LDA**-detectable, donor-reactive CTL accumulating in sponge matrix allografts; (2) failure to interfere with in vitro assays of cellular alloimmunity, including **LDA**; and (3) antigen non-specific **depression** of **LDA**-detectable CTL in lymph nodes, spleen and especially in peripheral blood. For peripheral blood CTL, the drug eliminated **LDA**-detectable CTL, an effect that was reversible and could not be attributed to the activation of suppressor cells. Since Ro23-6457 has little effect on the number of peripheral blood Thy1.2+ cells, it appears that this drug does not phys. eliminate CTL, but makes then temporarily hyporesponsive to antigen stimulation, and thus undetectable in functional assays like **LDA**.

L27 ANSWER 25 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1991:483740 HCAPLUS

DOCUMENT NUMBER: 115:83740

TITLE: Study on the dynamical spin susceptibility of paramagnetic lanthanum copper oxide (La₂CuO₄)

AUTHOR(S): Winter, H.; Szotek, Z.; Temmerman, W. M.

CORPORATE SOURCE: Daresbury Lab., Sci. Eng. Res. Counc., Daresbury, UK

SOURCE: Report (1989), DL/SCI/P-660T; Order No. PB90-209107, 21 pp. Avail.: NTIS

From: Gov. Rep. Announce. Index (U. S.) 1990, 90(14), Abstr. No. 037,702

DOCUMENT TYPE: Report

LANGUAGE: English

AB The one electron wave functions and energy bands obtained by the self-consistent LMTO-ASA methods in the local d. approximation are used to calculate the wavevector and frequency dependent noninteracting spin susceptibility of paramagnetic La₂CuO₄ in the bct.-structure. The matrix elements effects lead to a substantial **depression** of the susceptibility, especially for wavevectors near the X-point. Whereas interband transition contributions turn out to be significant, Fermi surface nesting properties are of less importance. In contradiction to the impression given by spin polarized electronic structure calcns., the RPA-**LDA** approximation for the susceptibility predicts this substance to be far away from a magnetic phase transition, and some light is shed on the cause for this failure.

L27 ANSWER 26 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1991:462859 HCAPLUS

DOCUMENT NUMBER: 115:62859

TITLE: On the dynamical spin susceptibility of paramagnetic lanthanum copper oxide (La₂CuO₄)

AUTHOR(S): Winter, H.; Szotek, Z.; Temmerman, W. M.
 CORPORATE SOURCE: Kernforschungszent. Karlsruhe, Karlsruhe, D-7500, Germany
 SOURCE: Materials Research Society Symposium Proceedings (1990), 193(At. Scale Calc. Struct. Mater.), 3-8
 CODEN: MRSPDH; ISSN: 0272-9172
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB The self-consistent one-electron wave functions and energy bands obtained by the LMTO-ASA method within the local d. approximation (**LDA**) are used to calculate the wave vector and frequency dependent non-interaction spin susceptibility of paramagnetic La₂CuO₄ in the body-centered tetragonal (bct) structure. The tendency towards the antiferromagnetic instability is shown to be strongly dependent on the effects of the matrix elements which lead to a substantial **depression** of the susceptibility, especially near the X-point. The Fermi surface nesting properties, although important for the susceptibility, are by far not sufficient for the instability and the interband transitions turn out to be great significance. The results indicate that the susceptibility is at least 3 times too small to drive this system through a transition to the antiferromagnetic state, and possible reasons for this failure are discussed.

L27 ANSWER 27 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 1990:416519 HCAPLUS
 DOCUMENT NUMBER: 113:16519
 TITLE: A study on the dynamic spin susceptibility of paramagnetic lanthanum copper oxide (La₂CuO₄)
 AUTHOR(S): Winter, H.; Szotek, Z.; Temmerman, W. M.
 CORPORATE SOURCE: INFP, Kernforschungszent. Karlsruhe, Karlsruhe, Germany
 SOURCE: Zeitschrift fuer Physik B: Condensed Matter (1990), 79(2), 241-9
 CODEN: ZPCMDN; ISSN: 0722-3277
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB The one electron wavefunctions and energy bands obtained by using the self-consistent LMTO-ASA (linearized muffin-tin orbital-atomic-sphere approximation) method in the local d. approximation (**LDA**) are used to calculate the wavevector and frequency dependent noninteracting spin susceptibility of paramagnetic La₂CuO₄ in the body-centered tetragonal structure. It is shown that matrix elements effects lead to a substantial **depression** of the susceptibility, especially for wavevectors near the X-point. Whereas interband transition contributions turn out to be significant, Fermi surface nesting properties are shown to be of less importance. In contradiction to the impression given by spin polarized electronic structure calcns. the RPA-**LDA** approximation for the susceptibility predicts this substance to be far away from a magnetic phase transition, and some light is shed on the cause for this failure.

L27 ANSWER 28 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 1989:141232 HCAPLUS
 DOCUMENT NUMBER: 110:141232
 TITLE: Composition for hair treatment comprising a calcium-chelating agent and a polymer
 INVENTOR(S): Watanabe, Taichi; Ogino, Hidekazu; Hirota, Hajime; Koshika, Tomohito; Moriya, Naoko; Nozaki, Toshio
 PATENT ASSIGNEE(S): Kao Corp., Japan
 SOURCE: Eur. Pat. Appl., 27 pp.
 CODEN: EPXXDW
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|--|------|----------|-----------------|----------|
| EP 269107 | A2 | 19880601 | EP 1987-117484 | 19871126 |
| EP 269107 | A3 | 19891011 | | |
| R: AT, CH, DE, ES, FR, GB, LI, NL | | | | |
| JP 63135318 | A2 | 19880607 | JP 1986-283745 | 19861128 |
| JP 06018770 | B4 | 19940316 | | |
| JP 63150212 | A2 | 19880622 | JP 1986-297897 | 19861215 |
| JP 63154612 | A2 | 19880627 | JP 1986-299673 | 19861216 |
| JP 06021052 | B4 | 19940323 | | |
| US 5009813 | A | 19910423 | US 1989-344443 | 19890427 |
| PRIORITY APPLN. INFO.: | | | JP 1986-283745 | 19861128 |
| | | | JP 1986-297897 | 19861215 |
| | | | JP 1986-299673 | 19861216 |
| | | | US 1987-122454 | 19871119 |
| AB A composition for hair treatment comprises a chelating agent for Ca ²⁺ and cationic polymers containing quaternary N or a peptide of an average mol. weight of 400 to 10,000, or their derivs. The composition provides a perm-treatment with a good finishing effect by depressing the absorption of Ca by the hair. It also serves as a shampoo, but further formulating with an anionic or amphoteric surface active agent, which gives an excellent effect of suppleness and smoothness, after washing and rinsing, to hair which had been damaged from a perm treatment. A shampoo comprised Na polyethylene lauryl sulfate 20, EDTA 1, Polymer OR 400 (cationized cellulose) 0.1, and lauric acid diethanolamide 3 parts, the balance being water. | | | | |

L27 ANSWER 29 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1977:25504 HCAPLUS

DOCUMENT NUMBER: 86:25504

TITLE: Atomic absorption spectrophotometry of europium using an enhancing effect of ammonium perchlorate

AUTHOR(S): Oguro, Hiroshi

CORPORATE SOURCE: Cent. Res. Lab., Matsushita Electr. Ind. Co., Ltd., Moriguchi, Japan

SOURCE: Bunseki Kagaku (1976), 25(7), 468-73
CODEN: BNSKAK; ISSN: 0525-1931

DOCUMENT TYPE: Journal

LANGUAGE: Japanese

AB In the atomic absorption spectrophotometry of Eu in an air-acetylene flame, NH₄ClO₄ increases the atomic absorption of Eu. In the case of 0.5M NH₄ClO₄, the increase is .apprx.1.5-fold. A method for eliminating the interferences of many coexisting compds. by using this enhancing effect and a method for determining Eu₂O₃ in La₂O₃ were investigated. The working conditions were: wavelength 4594 Å, lamp current 15 mA, burner height 10 mm, air flow-rate 6.5 l./min, acetylene flow-rate 1.8 l./min. Though the enhancing or **depressing** effects of HCl, HNO₃, HBr, and HClO₄ in concns. below 0.1M were eliminated by 0.5M NH₄ClO₄, the remarkable **depressing** effects of H₂SO₄ and H₃PO₄ on Eu could not be eliminated. The interferences of Na⁺, K⁺, Cs⁺, and Al³⁺, 200 ppm, were not eliminated, but those of other cations including rare earth elements were completely eliminated. **La 2000-10000 ppm** increased the absorption of Eu .apprx.1.4-fold. But the effect of La in the range 0-9000 ppm was also eliminated by NH₄ClO₄. The calibration curve for Eu in the presence of NH₄ClO₄ was linear in the range 0-400 ppm with a sensitivity larger by .apprx.1.5-fold than that for Eu alone. For practical samples, the values obtained were in fair agreement with those by the flame emission method by using a nitrous oxide-acetylene flame. The relative standard deviation of the method was 2.4-3.7% for 1-3% Eu₂O₃.

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 DICTIONARY FILE UPDATES: 26 OCT 2004 HIGHEST RN 769912-90-5

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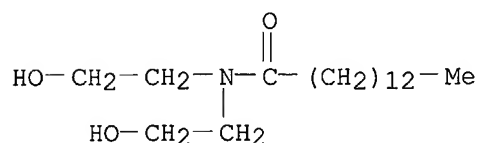
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L5 ANSWER 1 OF 3 REGISTRY COPYRIGHT 2004 ACS on STN
 RN 124767-08-4 REGISTRY
 CN Tetradecanamide, N,N-bis(2-hydroxyethyl)-, polymer with
 N,N-bis(2-hydroxyethyl)dodecanamide and 2,5-furandione (9CI) (CA INDEX
 NAME)
 OTHER CA INDEX NAMES:
 CN 2,5-Furandione, polymer with N,N-bis(2-hydroxyethyl)dodecanamide and
 N,N-bis(2-hydroxyethyl)tetradecanamide (9CI)
 CN Dodecanamide, N,N-bis(2-hydroxyethyl)-, polymer with N,N-bis(2-
 hydroxyethyl)tetradecanamide and 2,5-furandione (9CI)
 OTHER NAMES:
 CN **lauric acid diethanolamide-maleic anhydride-myristic acid**
diethanolamide copolymer
 MF (C18 H37 N O3 . C16 H33 N O3 . C4 H2 O3)x
 CI PMS
 PCT Polyamine, Polyester, Polyester formed, Polyvinyl
 SR CA
 LC STN Files: CA, CAPLUS, USPATFULL
 DT.CA Caplus document type: Patent
 RLD.P Roles for non-specific derivatives from patents: PREP (Preparation)

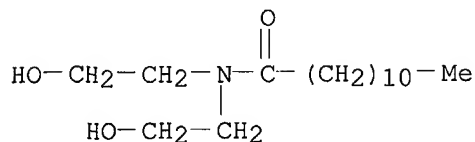
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CRN 7545-23-5
 CMF C18 H37 N O3



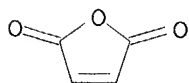
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CRN 120-40-1
CMF C16 H33 N O3



CM 3

CRN 108-31-6
CMF C4 H2 O3



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 112:36787

L5 ANSWER 2 OF 3 REGISTRY COPYRIGHT 2004 ACS on STN
RN 7487-79-8 REGISTRY
CN Dodecanoic acid, compd. with 2,2'-iminobis[ethanol] (1:1) (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN Ethanol, 2,2'-iminobis-, dodecanoate (salt) (9CI)
CN Ethanol, 2,2'-iminodi-, compd. with lauric acid (1:1)
CN Ethanol, 2,2'-iminodi-, laurate (salt) (8CI)
CN Lauric acid, compd. with 2,2'-iminodiethanol (7CI)
CN Lauric acid, compd. with 2,2'-iminodiethanol (1:1) (8CI)

OTHER NAMES:

CN Diethanolamine monolaurate
CN Lauric acid diethanolamine salt
CN **Lauric diethanolamine**
MF C12 H24 O2 . C4 H11 N O2
LC STN Files: CA, CAOLD, CAPLUS, CHEMLIST, HSDB*, IFICDB, IFIPAT, IFIUDB, TOXCENTER, USPATFULL

(*File contains numerically searchable property data)

Other Sources: DSL**, EINECS**, TSCA**

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DT.CA Caplus document type: Conference; Journal; Patent
RL.P Roles from patents: BIOL (Biological study); PROC (Process); PRP (Properties); USES (Uses)
RLD.P Roles for non-specific derivatives from patents: USES (Uses)
RL.NP Roles from non-patents: BIOL (Biological study); PRP (Properties); USES (Uses); NORL (No role in record)

CM 1

CRN 143-07-7
CMF C12 H24 O2

HO₂C-(CH₂)₁₀-Me

CM 2

CRN 111-42-2
CMF C4 H11 N O2

HO-CH₂-CH₂-NH-CH₂-CH₂-OH

42 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
42 REFERENCES IN FILE CAPLUS (1907 TO DATE)
1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 140:292641

REFERENCE 2: 138:289392

REFERENCE 3: 136:371022

REFERENCE 4: 136:324353

REFERENCE 5: 136:162584

REFERENCE 6: 136:39982

REFERENCE 7: 134:354846

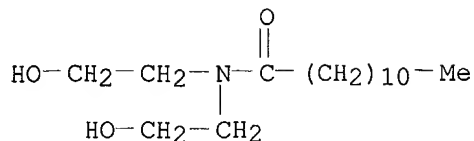
REFERENCE 8: 133:358827

REFERENCE 9: 133:165461

REFERENCE 10: 131:131549

L5 ANSWER 3 OF 3 REGISTRY COPYRIGHT 2004 ACS on STN
RN 120-40-1 REGISTRY
CN Dodecanamide, N,N-bis(2-hydroxyethyl)- (6CI, 8CI, 9CI) (CA INDEX NAME)
OTHER NAMES:
CN AC 1000
CN AC 1000 (amide)
CN Alkamide LE
CN Aminon L 02
CN Amisol LDE
CN Amisol SG
CN Bis(2-hydroxyethyl)lauramide
CN Chemistat 2500
CN Chemstat LD 100
CN Clindrol 100L
CN Clindrol 200L
CN Clindrol Superamide 100L
CN Comperlan LD
CN Condensate PL
CN Crillon LDE
CN Dehydat 10
CN Denone 2863
CN Detergent 6501
CN Diethanolamine lauroylamide

CN Diethanollauramide
 CN Duspar LA 2000
 CN Emid 6511
 CN Empilan LDE
 CN Ethylan MLD
 CN Hetamide ML
 CN Incromide LR
 CN LA 2000
 CN Lalmin D
 CN Lankrostat JP
 CN Lauramide DEA
 CN Lauramido DEA
 CN **Lauric acid diethanolamide**
 CN **Lauric diethanolamide**
 CN Lauroyl diethanolamide
 CN Lauroyldiethanolamine
 CN Lauryl diethanolamide
 CN LDA
 CN LDA (surfactant)
 CN LDE
 CN Mackamide LL
 CN Mackamide LLM
 CN Mazamide LS 196
 CN Monamid 150LW
 CN Monamid 150LWA
 CN N,N-Bis(β -hydroxyethyl)lauramide
 CN N,N-Bis(2-hydroxyethyl)dodecanamide
 CN N,N-Bis(2-hydroxyethyl)lauramide
 CN N,N-Bis(2-hydroxyethyl)lauroylamide
 CN N,N-Bis(2-hydroxyethyl)laurylamide
 CN N,N-Bis(hydroxyethyl)lauramide
 ADDITIONAL NAMES NOT AVAILABLE IN THIS FORMAT - Use FCN, FIDE, or ALL for
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 MF C16 H33 N O3
 CI COM
 LC STN Files: AGRICOLA, BEILSTEIN*, BIOBUSINESS, BIOSIS, CA, CAOLD, CAPLUS,
 CASREACT, CHEMCATS, CHEMLIST, CIN, CSCHEM, CSNB, HSDB*, IFICDB, IFIPAT,
 IFIUDB, IPA, MEDLINE, MSDS-OHS, NIOSHTIC, PIRA, PROMT, RTECS*, SPECINFO,
 TOXCENTER, USPAT2, USPATFULL
 (*File contains numerically searchable property data)
 Other Sources: DSL**, EINECS**, TSCA**
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 DT.CA CAplus document type: Conference; Journal; Patent; Report
 RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study);
 MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC
 (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses);
 NORL (No role in record)
 RLD.P Roles for non-specific derivatives from patents: BIOL (Biological
 study); PREP (Preparation); USES (Uses)
 RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological
 study); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC
 (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses);
 NORL (No role in record)
 RLD.NP Roles for non-specific derivatives from non-patents: BIOL (Biological
 study); PREP (Preparation); USES (Uses)



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 11 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
 1411 REFERENCES IN FILE CAPLUS (1907 TO DATE)
 61 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 141:299660
 REFERENCE 2: 141:297468
 REFERENCE 3: 141:279181
 REFERENCE 4: 141:279139
 REFERENCE 5: 141:264180
 REFERENCE 6: 141:226875
 REFERENCE 7: 141:209095
 REFERENCE 8: 141:179216
 REFERENCE 9: 141:179197
 REFERENCE 10: 141:175890

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 FILE LAST UPDATED: 26 Oct 2004 (20041026/ED)

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=> d stat que
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/CN OR "LAURIC ACID DIETHANOLAMIDE-MALEIC ANHYDRIDE-MYRISTIC
ACID DIETHANOLAMIDE COPOLYMER"/CN)
L4      2 SEA FILE=REGISTRY ABB=ON  PLU=ON  ("LAURIC DIETHANOLAMIDE"/CN
OR "LAURIC DIETHANOLAMINE"/CN)
L5      3 SEA FILE=REGISTRY ABB=ON  PLU=ON  L3 OR L4
L6      SEL  PLU=ON  L5 1- CHEM :      103 TERMS
L7      7064 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L6
L8      88622 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ("NERVOUS SYSTEM, DISEASE"/CV
OR "DISEASE, ANIMAL"/CV OR "DISEASES, BY BODY PART (NON-CA
HEADING)/CV OR "ORGAN, ANIMAL, DISEASE"/CV OR "BRAIN,
DISEASE"/CV OR "MENTAL DISORDER"/CV OR "MENTAL DISORDER (L)
DEMENTIA"/CV OR "DEMENTIA/CV OR "DEMENTIA MENTAL DISORDER"/CV)
L9      107784 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "NERVOUS SYSTEM, DISEASE"/CV
OR "BRAIN, DISEASE"/CV OR "MENTAL DISORDERS"/CV OR "PSYCHIATRY/C
V OR "ALZHEIMER'S DISEASE"/CV OR "AMNESIA/CV OR "BRAIN,
DISEASE (L) MULTI-INFARCT DEMENTIA"/CV OR "HYSTERIA/CV OR
INSOMNIA/CV OR "MENKES' SYNDROME"/CV OR "MENTAL RETARDATION"/CV
OR "AMAUROTIC FAMILIAL IDIOCY"/CV OR "AMAUROTIC FAMILIAL
IDIOCY (L) CEROID LIPOFUSCINOSIS, NEURONAL"/CV OR "CHROMOSOME
(L) HUMAN X, DISEASE, FRAGILE"/CV OR "COCKAYNE'S SYNDROME"/CV
OR "DOWN'S SYNDROME"/CV OR "FRAGILE X SYNDROME"/CV OR "GANGLIOSI
DOSIS/CV OR "AMAUROTIC FAMILIAL IDIOCY (L) INFANTILE"/CV OR
"SANDHOFF'S DISEASE"/CV OR "LESCH-NYHAN SYNDROME"/CV OR
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LIPOFUSCINOSIS"/CV OR "AMAUROTIC FAMILIAL IDIOCY (L) JUVENILE"/
CV OR "NIEMANN-PICK DISEASE"/CV OR "PHENYLKETONURIA/CV OR
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OR "ELECTROCONVULSIVE THERAPY"/CV OR "HYPNOTICS AND SEDATIVES"/
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OR "ISOBUTYL IODIDE"/CV)
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L11     69417 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ("NERVOUS SYSTEM, DISEASE"/CV
OR "MOVEMENT DISORDERS"/CV OR "PARKINSON'S DISEASE"/CV OR
PARKINSONISM/CV OR "LEWY BODY DISEASE"/CV OR "RAMSAY HUNT
PARALYSIS SYNDROME"/CV OR "PARKINSONISM (L) GUAMANIAN PARKINSON
ISM-DEMENTIA"/CV OR "PARKINSONISM (L) HEMI"/CV OR "ANTIPARKINSON
IAN AGENTS"/CV OR "TREMOR/CV OR "A-SYNUCLEIN/CV OR
"1,2,3,6-TETRAHYDRO-1-METHYL-4-PHENYLPYRIDINE"/CV OR "1-METHYL-4
-PHENYLPYRIDINIUM/CV OR "6-HYDROXYDOPAMINE/CV OR "DOPAMINE/CV)
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L14     43444 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ("AGING, ANIMAL"/CV OR
"AGING, ANIMAL (L) SENILITY"/CV OR "SENESCENCE (L) SENILITY"/CV
OR "SENESCENCE AND SENILITY"/CV OR "SENILITY/CV)
L15     236064 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L12 OR L14
L16     28543 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (EMOTION/CV OR "ANXIETY/CV OR
ANXIETIES/CV OR "MOOD/CV OR "ANXIOLYTICS/CV OR "NERVOUS SYSTEM
DEPRESSANTS"/CV OR "STRESS, ANIMAL"/CV)
L17     256779 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L15 OR L16
L18     35017 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ("STRESS, BIOLOGICAL"/CV OR
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"STRESS, ANIMAL"/CV OR "STRESS, ANIMAL (L) JET LAG"/CV OR "JET LAG"/CV OR "JET LAG SYNDROME"/CV)
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 L23 27 SEA FILE=HCAPLUS ABB=ON PLU=ON L7(L) (JET(W)LAG OR ?MELANCO?
 OR ?DEPRESS? OR ?SENIL? OR ?DEMENTI? OR ?INSOM? OR ?PARKIN? OR
 ?ALZHE? OR ?ANXIET?)
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 L27 29 SEA FILE=HCAPLUS ABB=ON PLU=ON L23 OR L25
 L28 38 SEA FILE=HCAPLUS ABB=ON PLU=ON (L7 AND (L19 OR L23)) NOT L27

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L28 ANSWER 1 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2004:701975 HCAPLUS
 DOCUMENT NUMBER: 141:225304
 TITLE: Preparation of cyclohexyl-substituted lactams as
 cytokine receptor modulating agents
 INVENTOR(S): Cherney, Robert J.; Carter, Percy; Duncia, John V.;
 Gardner, Daniel S.; Santella, Joseph B.
 PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA
 SOURCE: PCT Int. Appl., 385 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-------------------|------------|
| WO 2004071460 | A2 | 20040826 | WO 2004-US4418 | 20040211 |
| W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ, MZ, NA, NI RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 2004186140 | A1 | 20040923 | US 2004-776828 | 20040211 |
| PRIORITY APPLN. INFO.: | | | US 2003-446850P | P 20030212 |
| OTHER SOURCE(S): | | | MARPAT 141:225304 | |
| GI | | | | |

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Cyclohexyl-substituted lactams I [A = (un)substituted saturated or partially saturated cycloalkyl or heterocycloalkyl group with 3-8 atoms; E = S(:O)pCHR3, CHR3NR3, C(:O)NR3, N(R3)C(:O)NR3, SO2N(R3), N(R3)SO2N(R3); G = (CHR10)n; J = CH2CH2, CH:CH un(substituted) with (R13)s; R1, R2 = (un)substituted aryl or heteroaryl ring; R3 = H, alkyl; R10 = H, (un)substituted alkyl (two R10 groups may together comprise a carbonyl group); R11, R12 (independently) =

H, (un)substituted alkyl, aralkyl, heteroaralkyl, ϵ -hydroxyalkyl, ϵ -mercaptoalkyl, ϵ -alkoxyalkyl, etc.; R13 = H, (un)substituted alkyl; X = O, S; Z = bond, (un)substituted aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminosulfonyl, aminosulfonylamino, carbonylamino, oxycarbonylamino, aminocarbonyloxy, alkenediyl, methylene, etc.; m = 0-1; n = 0-3; s = 0-1] such as II are prepared as modulators of cytokine activity for the treatment of diseases associated with cytokines and their receptors such as inflammation, osteo- and rheumatoid arthritis, autoimmune diseases, HIV infection, inflammatory bowel disease, asthma, multiple sclerosis, and atherosclerosis. E.g., 1,4-cyclohexanedione mono(ethylene ketal) is lithiated and acylated with Et cyanoformate, reductively aminated with (S)- α -methylbenzylamine, subjected to reduction with lithium aluminum hydride followed by hydrogenolysis with palladium hydroxide and protection with Cbz anhydride to yield nonracemic III. E.g., III undergoes substitution at the primary carbon with 4-bromophenyl disulfide and tributylphosphine followed by oxidation with mCPBA, Stille methylation of the p-bromophenyl moiety, hydrogenolysis of the Cbz protecting group, acylation with N-Cbz-L-methionine, and S-methylation and cyclization with Me iodide and cesium carbonate to yield IV. E.g., IV undergoes acid-catalyzed deketalization, titanium-mediated Meerwein-Ponndorf-Verley reduction with isopropylamine (giving a mixture of both epimers at the amine center), N-methylation with formaldehyde and sodium triacetoxyborohydride, hydrogenolysis of the Cbz protecting group on the aminopyrrolidinone, and acylation with 3-trifluoromethylbenzoic acid and HATU to yield II. The compds. are modulators of chemokine receptor activity (no data). In addition, methods of halolactamization and dehalogenation and reagents appropriate for such transformations are claimed.

L28 ANSWER 2 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2004:550958 HCAPLUS

DOCUMENT NUMBER: 141:106465

TITLE: Preparation of substituted pyrrolo-pyrazole derivatives as kinase inhibitors

INVENTOR(S): Brasca, Maria Gabriella; Amici, Raffaella; Fancelli, Daniele; Nesi, Marcella; Orsini, Paolo; Orzi, Fabrizio; Roussel, Patrick; Vulpetti, Anna; Pevarello, Paolo

PATENT ASSIGNEE(S): Pharmacia Italia S.p.A., Italy

SOURCE: PCT Int. Appl., 116 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------|--|----------|-----------------|----------|
| WO 2004056827 | A2 | 20040708 | WO 2003-EP50942 | 20031204 |
| W: | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD | | | |
| RW: | BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | |

PRIORITY APPLN. INFO.: US 2002-434952P P 20021219

OTHER SOURCE(S): MARPAT 141:106465

GI

L28 ANSWER 3 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:102964 HCAPLUS
DOCUMENT NUMBER: 141:187239
TITLE: Probabilistic Disease Classification of
Expression-Dependent Proteomic Data from Mass
Spectrometry of Human Serum
AUTHOR(S): Lilien, Ryan H.; Farid, Hany; Donald, Bruce R.
CORPORATE SOURCE: Dartmouth Computer Science Department, Dartmouth
Medical School, Hanover, NH, 03755, USA
SOURCE: Journal of Computational Biology (2003), 10(6),
925-946
CODEN: JCOBEM; ISSN: 1066-5277
PUBLISHER: Mary Ann Liebert, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

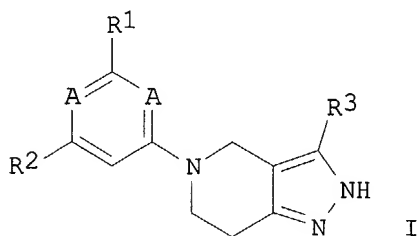
Page 35

method outperforms previous full-spectrum complex sample spectral classification techniques and can provide clues as to the mol. identities of differentially expressed proteins and peptides.

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 4 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2003:972075 HCAPLUS
 DOCUMENT NUMBER: 140:27838
 TITLE: Preparation of pyrazolo[4,3-c]pyridinyl substituted pyrimidinamines as inhibitors of JAK and CDK2 protein kinases
 INVENTOR(S): Ledford, Brian E.
 PATENT ASSIGNEE(S): Vertex Pharmaceuticals Incorporated, USA
 SOURCE: PCT Int. Appl., 40 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|------------------|------------|
| WO 2003101989 | A1 | 20031211 | WO 2003-US16900 | 20030530 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 2003236244 | A1 | 20031225 | US 2003-449742 | 20030530 |
| PRIORITY APPLN. INFO.: | | | US 2002-384538P | P 20020530 |
| OTHER SOURCE(S): | | | MARPAT 140:27838 | |
| GI | | | | |



AB The title compds. [I; A = N, CH, provided that at least one A = N; R1, R2 = halo, CN, NO2, (un)substituted OH, etc.; R3 = (un)substituted 3-8 membered monocyclic or 8-10 membered bicyclic (un)saturated ring, 3-7 membered heterocyclic ring having 1-3 heteroatoms selected from N, O, or S, 5-6 membered monocyclic or 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms selected from N, O or S; with provisos] which are inhibitors of protein kinases, particularly inhibitors of JAK and CDK2 mammalian protein kinases, and therefore are useful in the treatment of various protein kinase mediated disorders, were prepared Thus, treating benzylpiperidone with LDA in THF followed by addition of m-anisoyl chloride, treatment of intermediate with N2H4, benzyl-group removal, and reaction of the amine with 6-chloro-2-methylsulfanylpurimidin-4-ylamine

afforded I [A = N; R1 = SMe; R2 = NH2; R3 = 2-MeOC6H4]. It was claimed that compds. I were shown to inhibit JAK and CDK2 kinases (no data). The invention also provides pharmaceutically acceptable compns. comprising the compds. I.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 5 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:796662 HCAPLUS

DOCUMENT NUMBER: 139:292159

TITLE: Preparation of (1-indanone)-(1,2,3,6-tetrahydropyridine) derivative for use as sigma receptor agonists

INVENTOR(S): Iimura, Yoichi; Kosasa, Takashi; Yamanishi, Yoshiharu

PATENT ASSIGNEE(S): Eisai Co., Ltd., Japan

SOURCE: PCT Int. Appl., 47 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| WO 2003082820 | A1 | 20031009 | WO 2003-JP3630 | 20030325 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |

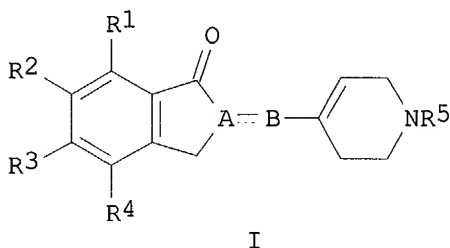
PRIORITY APPLN. INFO.:

JP 2002-95352

A 20020329

OTHER SOURCE(S): MARPAT 139:292159

GI



AB The patent relates to the preparation of an excellent sigma receptor binder and/or acetylcholine esterase inhibitor which contains a (1-indanone)-(1,2,3,6-tetrahydropyridine) derivative (I), a pharmacol. acceptable salt thereof, or a hydrate of either. wherein R1, R2, R3, R4 = H, halogen, OH, alkyl, alkoxy etc.; R5 = H, alkyl, cycloalkyl etc.; and A, B = partial structure of >C=CH-(CH2)m- or >C(R6)-(CH2)m- where R6 = H, halogen, OH, alkyl, alkoxy etc.; and m = 0-5. Thus, 1-benzyl-4-[(5,6-diethoxy-2-fluoro-1-indanone)-2-yl]methyl-1,2,3,6-tetrahydropyridine hydrochloride prepared by fluorination of 1-benzyl-4-[(5,6-diethoxy-1-indanone)-2-yl]methyl-1,2,3,6-tetrahydropyridine with N-

fluorobenzenesulfonimide using lithium bis(trimethylsilyl)amide as a base, showed acetylcholine esterase inhibition rate (IC50) of 0.4 nM compared to 3.9 for the control (donepezil hydrochloride).

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 6 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:796483 HCAPLUS

DOCUMENT NUMBER: 139:292139

TITLE: Preparation of heteroarylalkanols as glucocorticoid mimetics for treatment of inflammatory, allergic, and proliferative diseases

INVENTOR(S): Bekkali, Younes; Betageri, Raj; Gilmore, Thomas A.; Cardozo, Mario G.; Kirrane, Thomas M.; Kuzmich, Daniel; Proudfoot, John Robert; Takahashi, Hidenori; Thomson, David; Wang, Ji; Zindell, Renee; Harcken, Christian Hanke Justus Joachim; Riether, Doris

PATENT ASSIGNEE(S): Boehringer Ingelheim Pharmaceuticals, Inc., USA

SOURCE: PCT Int. Appl., 277 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

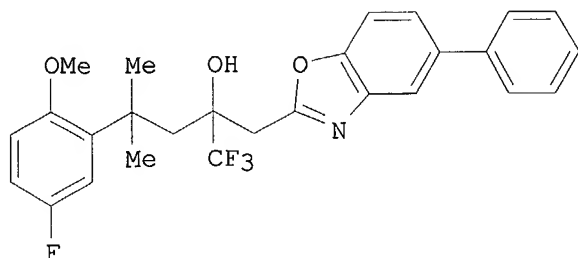
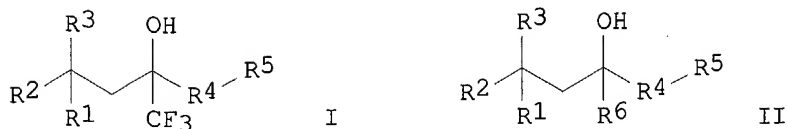
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|------------|
| WO 2003082280 | A1 | 20031009 | WO 2003-US8901 | 20030321 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 2004023999 | A1 | 20040205 | US 2003-394303 | 20030321 |
| PRIORITY APPLN. INFO.: | | | US 2002-367758P | P 20020326 |
| | | | US 2002-431817P | P 20021209 |
| | | | US 2003-442404P | P 20030124 |

OTHER SOURCE(S): MARPAT 139:292139

GI

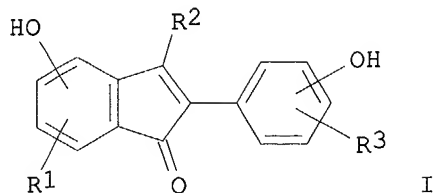


AB Title compds. I and II [wherein R1 = substituted (hetero)aryl; R2 and R3 = independently H or alkyl; or CR2R3 = cycloalkyl; R4 = (un)substituted alkyl, alkenyl, or alkynyl; R5 = substituted heteroaryl; and R6 (when present) = (un)substituted alkyl, alkenyl, alkynyl, carbocyclyl(alkyl), heterocyclyl(alkyl), (hetero)aryl(alkyl), arylhaloalkyl, carbocyclylalkenyl, heterocyclylalkenyl, or (hetero)arylalkenyl; and tautomers, prodrugs, solvates, or salts thereof] were prepared as glucocorticoid mimetics (no data). For example, 1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-one (multi-step preparation from Et trifluoropyruvate, 1-bromo-2-methylpropene, and 4-fluoroanisole given) was coupled with 2-methyl-5-phenylbenzoxazole using **LDA** in THF to afford III. I, II, and pharmaceutical compns. containing such compds. are useful for treating inflammatory, allergic, or proliferative disorders mediated by glucocorticoid receptor (GR) function (no data).

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 7 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:696535 HCAPLUS
DOCUMENT NUMBER: 139:230484
TITLE: Preparation of substituted indenones as estrogenic
agents
INVENTOR(S): Mcdevitt, Robert E.; Adebi, Folake O.; Harris, Heather
A.; Keith, James C.; Albert, Leo M.
PATENT ASSIGNEE(S): Wyeth, John, and Brother Ltd., USA
SOURCE: U.S. Pat. Appl. Publ., 24 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|--------|------------|-----------------|------------|
| ----- | --- | ----- | ----- | ----- |
| US 2003166643 | A1 | 20030904 | US 2002-316446 | 20021211 |
| PRIORITY APPLN. INFO.: | | | US 2001-341188P | P 20011213 |
| OTHER SOURCE(S): | MARPAT | 139:230484 | | |
| GI | | | | |



AB The title compds. [I; R1 = H, OH, halo, etc.; R2 = H, OH, alkyl, etc.; R3 = H, halo, OH, etc.] which are estrogen receptor modulators, were prepared and formulated. Thus, reacting Me 4-methoxybenzoate with 4-methoxyphenylacetonitrile in the presence of **LDA** in THF followed by treatment of the intermediate with BBr₃ afforded 3-amino-5-hydroxy-2-(4-hydroxyphenyl)-1H-inden-1-one which showed IC₅₀ of 1.15 μ M against ER- β binding and IC₅₀ of > 5.0 μ M against ER- α binding. Pharmaceutical composition comprising the title compound I was claimed.

L28 ANSWER 8 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:649147 HCAPLUS

DOCUMENT NUMBER: 140:122079

TITLE: Symmetry considerations in Markovian chemicals in silico' design (MARCH-INSIDE) I: central chirality codification, classification of ACE inhibitors and prediction of σ -receptor antagonist activities

AUTHOR(S): Diaz, Humberto Gonzalez; Sanchez, Ivan Hernandez; Uriarte, Eugenio; Santana, Lourdes

CORPORATE SOURCE: Chemical Bio-actives Center, Central University of Las Villas, Santa Clara, 54830, Cuba

SOURCE: Computational Biology and Chemistry (2003), 27(3), 217-227

CODEN: CBCOCH; ISSN: 1476-9271

PUBLISHER: Elsevier Science Ireland Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The Mar.-INSIDE methodol. has been generalized, by an exponential central symmetry factor, to codify chemical structure information for chiral drugs. To test the potential of this novel approach in drug design we have modeled the angiotensin-converting enzyme inhibitory activity of perindoprilate's σ -stereoisomer combinatorial library. A linear discriminant anal. (**LDA**) model classifies correctly 83.33% of active compds. and 94.12% of non-active ones in a training set, results that represent a total of 91.3% accuracy in classification. The model classifies 83.33% of these compds. in the predicting series. Only three isomers (those with higher activity) were used in the predicting set and the model classified all three very well. Similar predictive behavior was observed in a leave-1-out cross validation experiment Canonical regression anal. corroborated the statistical quality of the models (R_{canc}=0.79, with a P-level<0.000) and was also used to compute biol. activity canonical scores for each compound Finally, prediction of the biol. activities of chiral 3-(3-hydroxyphenyl)piperidines, which are σ -receptor antagonists, by linear regression anal. was carried out. The model was statistically significant (R=0.963, S=0.29, P<0.00) and can be considered as a preliminary comparative study between Mar.-INSIDE and Chiral Topol. descriptors. Application of the Student test permits the detection of non-sym. properties within the data set and justified the requirement of non-sym. (for pairs of enantiomers) mol. descriptors. The Mar.-INSIDE model showed very good stability to data variation in the leave-1-out cross validation experiment (Scv=0.32).

REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 9 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2003:396850 HCAPLUS
 DOCUMENT NUMBER: 138:401597
 TITLE: Preparation of arylpyrrolidinones as neurokinin-1
 (NK1) antagonists.
 INVENTOR(S): Reichard, Gregory A.; Paliwal, Sunil; Shih, Neng-Yang;
 Xiao, Dong; Tsui, Hon-Chung; Shah, Sapna; Wang, Cheng;
 Wroblewski, Michelle L.
 PATENT ASSIGNEE(S): Schering Corporation, USA
 SOURCE: PCT Int. Appl., 81 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|--|----------|-----------------|------------|
| WO 2003042173 | A1 | 20030522 | WO 2002-US36186 | 20021112 |
| WO 2003042173 | C1 | 20031002 | | |
| W: | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SC, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UZ, VC, VN, YU, ZA, ZM | | | |
| RW: | GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | |
| US 2003144270 | A1 | 20030731 | US 2002-292618 | 20021112 |
| EP 1451153 | A1 | 20040901 | EP 2002-803200 | 20021112 |
| R: | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK | | | |
| PRIORITY APPLN. INFO.: | | | US 2001-337652P | P 20011113 |
| | | | WO 2002-US36186 | W 20021112 |
| OTHER SOURCE(S): | MARPAT 138:401597 | | | |
| GI | | | | |

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. [I; Q = (CR6R7)n2; X1 = O, S, SO, SO2, NR18a, N(COR12), N(SO2R15); X2 = C, S, SO; Y = O, S, NR11; R1, R2 = H, alkyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, CH2F, CHF2, CF3; R1R2 = alkylene, CO; R3 = alkyl, hydroxyalkyl, cycloalkyl, CH2F, CHF2, CF3; R4, R5 = (CR28R29)n1G, C(O)(CR28R29)n4G; n1 = 0-5; n2 = 1-4; n4 = 1-5; G = H, CF3, CHF2, CH2F, OH, alkoxy, SO2R13, cycloalkoxy, NR13R14, SO2NR13R14, NR13SO2R15, NR13COR12NR12(CONR13R14), NR12COC(R12)2NR13R14, CONR13R14, COOR12, cycloalkyl, (R19)r-aryl, (R19)r-heteroaryl, O2CR14, O2CNR13R14, etc.; R4R5 = CO, NR12, atoms to form 4-7 membered ring; R6 = H, alkyl, OR13, SR18; R7 = H, alkyl; R6R7 = CO; R12 = H, alkyl, cycloalkyl, cycloalkylalkyl; R13, R14 = H, alkyl, cycloalkyl, cycloalkylalkyl; R13R14 = atoms to form 4-7 membered ring; R18 = H, alkyl, cycloalkyl, cycloalkylalkyl, P(O)(OH)2; R18a = H, alkyl, cycloalkyl, cycloalkylalkyl; Ar1, Ar2 = (substituted) Ph, heteroaryl; R28, R29 = H, alkyl, CH2F, CHF2, CF3; with provisos], were prepared as NK1 antagonists (no data). Thus, aminoamide (II) was autoclaved with Ba(OH)2 in H2O at 155° followed by treatment (Boc)2O to give 96% Boc-protected acid. The latter in CH2Cl2 was treated with triphosgene and diisopropylethylamine to give 94% cyclic anhydride, which was

condensed with EtOAc using LDA in THF to give 88% acetoacetate derivative, which in CH₂Cl₂ was treated with HCl in dioxane to give title compound (III).

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 10 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2003:133002 HCAPLUS
 DOCUMENT NUMBER: 138:175870
 TITLE: Transdermal delivery of 5-HT₃ antagonists
 INVENTOR(S): Kamiyama, Fumio; Quan, Ying-Shu; Watkinson, Adam Charles
 PATENT ASSIGNEE(S): Strakan Group Limited, UK
 SOURCE: PCT Int. Appl., 80 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| WO 2003013482 | A1 | 20030220 | WO 2002-GB3571 | 20020802 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |

PRIORITY APPLN. INFO.: GB 2001-19012 A 20010803

AB Transdermal dressings have adhesives comprising a crosslinked block copolymer and a plasticizer, the block copolymer having hard and soft segments, there being chemical crosslinking between the soft segments, the plasticizer being present in an amount of at least 10% by weight of the adhesive, wherein the plasticizer is a high mol. weight, oily ester, are able to carry and deliver enhanced quantities of 5-HT₃ antagonists, especially ondansetron and granisetron. Thus, the highest flux of ondansetron was observed from patches containing ondansetron-HCl and octyldodecyl lactate.

IT **120-40-1, Lauric acid diethanolamide**

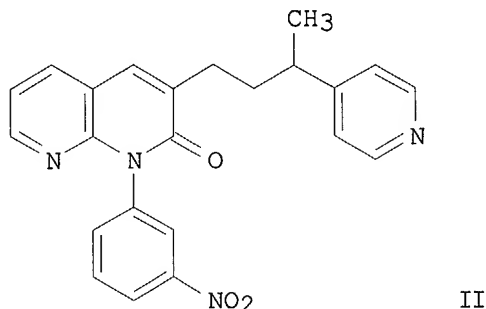
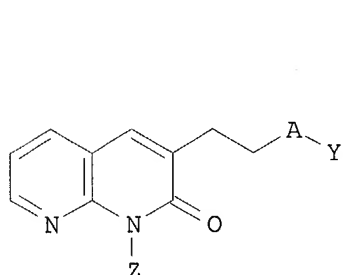
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (permeation enhancer; transdermal delivery of 5-HT₃ antagonists)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 11 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2002:964355 HCAPLUS
 DOCUMENT NUMBER: 138:55951
 TITLE: Preparation of 1-(2,1,3-benzothiadiazolyl)-3-pyridylpropyl-1,8-naphthyridine derivatives as phosphodiesterase (PDE) IV inhibitors
 INVENTOR(S): Aotsuka, Tomoji; Kumazawa, Kentarou; Wagatsuma, Nagatoshi; Ishitani, Kouki; Nose, Takashi
 PATENT ASSIGNEE(S): Grelan Pharmaceutical Co., Ltd., Japan
 SOURCE: PCT Int. Appl., 69 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|------------------|-----------------|----------|
| WO 2002100859 | A1 | 20021219 | WO 2002-JP5804 | 20020611 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG EP 1403270 A1 20040331 EP 2002-733476 20020611 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR US 2004176365 A1 20040909 US 2003-480378 20031211 PRIORITY APPLN. INFO.: JP 2001-176550 A 20010612 WO 2002-JP5804 W 20020611 | | | | |
| OTHER SOURCE(S): | | MARPAT 138:55951 | | |
| GI | | | | |



AB The title compds. I [wherein A = CH₂, alkyl-CH₂, CO, HOCH₂, or alkyl-CO₂CH₂; Y = heteroaryl; Z = heteroaryl or (un)substituted Ph] and pharmaceutically acceptable salts thereof are prep'd as PDE IV inhibitors for the treatment of asthma. For example, 2-(3-nitrophenylamino)nicotinaldehyde (prepn given) was reacted with Et 5-methyl-5-(pyrid-4-yl)pentanoate (prepn given) in THF in the presence of **LDA** to afford the naphthyridine II (37%). II showed IC₅₀ of 0.070 μM against PDE IV and ED₅₀ of 0.12 mg/kg against asthma in guinea pig.

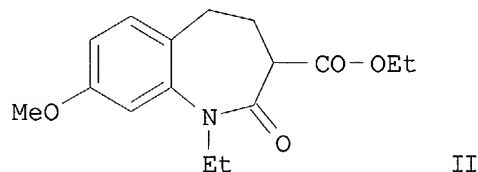
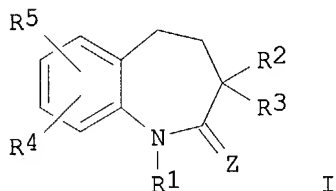
REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 12 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2002:964123 HCAPLUS
 DOCUMENT NUMBER: 138:24651
 TITLE: Preparation of substituted 1-benzazepines and derivatives thereof as antibacterial agents
 INVENTOR(S): Tomazic, Alenka; Huang, Liren; Clancy, Joanna
 PATENT ASSIGNEE(S): Antex Pharma, Inc., USA
 SOURCE: PCT Int. Appl., 200 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|--------------------------------------|------------|
| WO 2002100327 | A2 | 20021219 | WO 2002-US15214 | 20020515 |
| WO 2002100327 | A3 | 20030522 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| EP 1392317 | A2 | 20040303 | EP 2002-763196 | 20020515 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| PRIORITY APPLN. INFO.: | | | US 2001-290991P | P 20010516 |
| | | | WO 2002-US15214 | W 20020515 |
| OTHER SOURCE(S): | | | CASREACT 138:24651; MARPAT 138:24651 | |
| GI | | | | |



AB Substituted 1-benzazepines (shown as I; e.g. 3-ethoxycarbonyl-1-ethyl-8-methoxy-2,3,4,5-tetrahydro-1H-1-benzazepine-2-one (II)) were prepared and found be active as antibacterial agents. For I: R1 = H or (un)substituted (cyclo)alkyl, alkenyl, alkynyl, or Ar or (CH2)nAr, (CH2)mCOR, (CH2)nCN, (CH2)mC(Q)OR, CONR2, OR, SO2R, CONHNHR, CH2OR, (CH2)nOAr, (CH2)mC(NH)NH2, (CH2)nNHAr, CH2CH2C(O)NR6CH2C(O)NH2 (R6 = N,N-dimethylethylenediamino, 2-methoxyethylamino, benzylamino, 3-trifluormethylbenzylamino, cyclopropylamino, propylamino, allylamino, 3-methoxybenzylamino, 2-(4-methoxyphenyl)ethylamino, cyclohexanemethylamino, 2,4-dichlorophenethylamino, 3-diethylaminopropylamino, 3-ethoxypropylamino, N,N-dibutylethylenediamino, 1-(2-aminoethyl)piperidine, 1-(3-aminopropyl)imidazole, 4-(2-aminoethyl)morpholine, 2-(aminomethyl)-1-ethylpyrrolidine, 2-(2-aminoethyl)pyridine or 3-(aminomethyl)pyridine). R2 and R3 = independently H, halo, N3, CN, (un)substituted (cyclo)alkyl, alkenyl, alkynyl, or Ar or (CH2)nAr, (CH2)mNR2, (CH2)mNHAA, (CH2)mNC(O)R, (CH2)mCONHOR, (CH2)mCOOR, (CH2)mCONHAA, (CH2)mCONR2, (CH2)nCONHAA or CO2CH2CH2X (X = 2-methyl-5-nitroimidazol-1-yl). R4 and R5 = independently H (R4 and R5 not both H), halo, NO2, CN, (un)substituted (cyclo)alkyl, alkenyl, alkynyl, Ar, (CH2)nAr, primary or secondary amino, or NHC(O)R, QR, NHC(Q)NHCOOR, NHCQNHR, OCONR2, COOR, OSiR3, C(O)NR2, NHSO2R7 (R7 = 2,4-difluorophenyl, 2-fluorophenyl, 4-isopropylphenyl, 2,5-dimethoxyphenyl, 3,4-dichlorophenyl, 2,3,5,6-tetramethylphenyl, 2-chlorophenyl, 3-nitrophenyl, 4-acetylphenyl, 4-methyl-3-nitrophenyl, 4-butylphenyl, 4-nitrophenyl, 4-propylphenyl, 5-fluoro-2-methylphenyl,

4-chloro-2,5-dimethylphenyl). R = H or (un)substituted (cyclo)alkyl, alkenyl, alkynyl, Ar, or (CH₂)_nAr; Q = O or S; Z = O or S; m = 0-2; n = 1-3; Ar = (hetero)aryl, arylalkyl, or heterocyclyl; Aa = amino acid. For example, 7-methoxy-1-tetralone oxime (preparation given) was treated with P2O5 in MeSO₃H to provide 8-methoxy-2,3,4,5-tetrahydro-1H-1-benzazepine-2-one (73%). The benzazepine was stirred with di-Et pyrocarbonate in the presence of **LDA** in THF to give the 3-substituted product (34%), which was then alkylated with EtI in AcCN using Cs₂CO₃ to afford II (48%). In antibacterial activity testing by the broth dilution method, some I inhibited growth of bacteria significantly.

L28 ANSWER 13 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:804542 HCAPLUS

DOCUMENT NUMBER: 138:51283

TITLE: Possible Pleiotropic Effects of Genes Specifying Sedative/Hypnotic Sensitivity to Ethanol on Other Alcohol-Related Traits

AUTHOR(S): Owens, Jeremy C.; Bennett, Beth; Johnson, Thomas E.

CORPORATE SOURCE: Inst. Behav. Genet., Univ. Colorado, Boulder, CO, USA

SOURCE: Alcoholism: Clinical and Experimental Research (2002), 26(10), 1461-1467

CODEN: ACRSDM; ISSN: 0145-6008

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Initial sensitivity to ethanol is a predictor of alc. abuse that has been studied extensively in both human and animal populations. Selection for initial sensitivity to the sedative/hypnotic effects of ethanol resulted in the long-sleep and short-sleep lines of mice. Some of the genes selected in these lines could also specify differential responses in other ethanol-related phenotypes and, perhaps, for other drugs of abuse. The authors assessed congenic mice carrying a single quant. trait locus (QTL) from the inbred long-sleep (ILS) or inbred short-sleep (ISS) strain on the reciprocal background for a number of ethanol- and pentobarbital-related phenotypes. Each congenic strain was tested for ethanol elimination rates at 4.1 g/kg, ethanol-induced ataxia at 2.0 g/kg, ethanol-induced hypothermia at 4.1 g/kg, and pentobarbital-induced loss of righting reflex (LORR) at 60 mg/kg. Addnl., the ILS.ISS congenics were tested for low-dose ethanol-induced activation (**LDA**) at five doses ranging from 0.6 to 1.2 g/kg ethanol, and the ISS.ILS congenics were tested for **LDA** at 1.8 g/kg of ethanol. There was little difference in the ethanol elimination rate between congenics and background strains, although a modest sex effect was found, with the females eliminating ethanol more rapidly than the males. The authors were unable to replicate previous differences found in **LDA** for the congenic on the ISS background, because none of the congenics differed from controls for **LDA**. congenics showed a differential effect of pentobarbital-induced LORR in the expected directions. The congenics on the ISS background showed more ethanol-induced ataxia than the ISS controls. Addnl., the hypothermic response seems affected by and maybe others. At least two regions carrying a QTL specifying sensitivity to high doses of ethanol cospecify altered sensitivity in other measures of alc. action. Specifically, these QTLs clearly affect ethanol-induced hypothermia and pentobarbital-induced LORR and possibly ethanol-induced ataxia.

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 14 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN

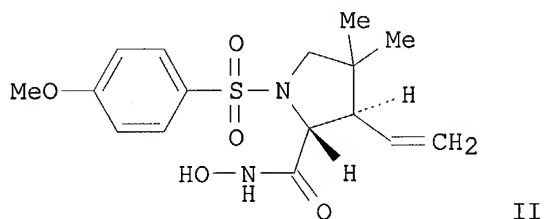
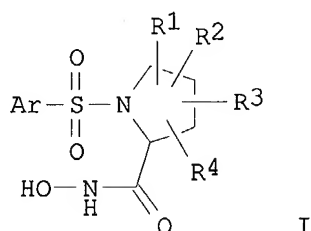
ACCESSION NUMBER: 2002:796616 HCAPLUS

DOCUMENT NUMBER: 137:279084

TITLE: Preparation of N-sulfonylpyrrolidine hydroxamic acids as MMP inhibitors

INVENTOR(S): Hanessian, Stephen; Moitessier, Nicolas; Mackay, Bruce; Hickman, John; Tucker, Gordon; Caignard, Daniel
 PATENT ASSIGNEE(S): Henri; Renard, Pierre
 Les Laboratoires Servier, Fr.
 SOURCE: Fr. Demande, 37 pp.
 CODEN: FRXXBL
 DOCUMENT TYPE: Patent
 LANGUAGE: French
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|-------------------|----------|-----------------|----------|
| FR 2819252 | A1 | 20020712 | FR 2001-312 | 20010111 |
| PRIORITY APPLN. INFO.: | | | FR 2001-312 | 20010111 |
| OTHER SOURCE(S): | MARPAT 137:279084 | | | |
| GI | | | | |



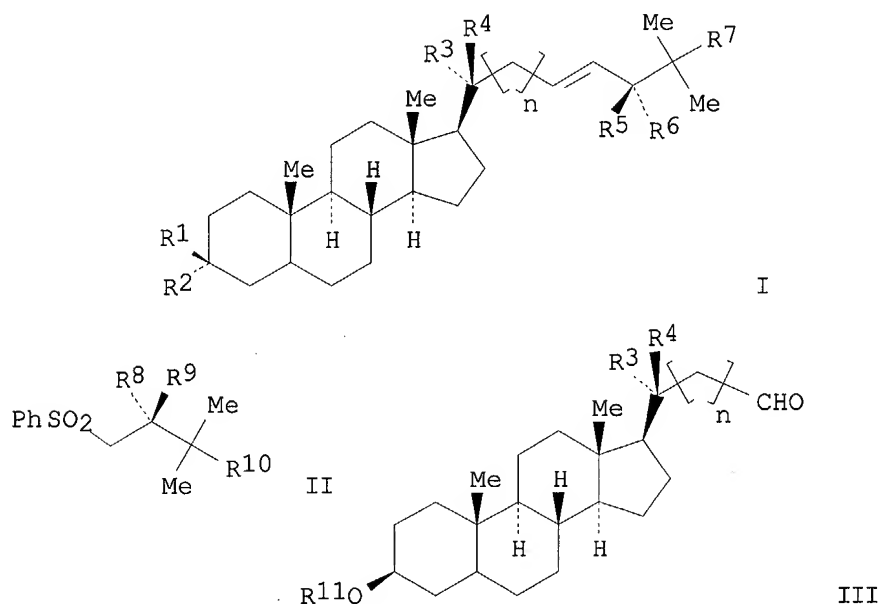
AB Title compds. I [$n = 0-2$; R_1 = alkylcarboxamido; R_2 = (hetero)arylalkyl; Ar = (hetero)aryl] were prepared. For instance, (+)-(5R)-5-((tert-Butyldiphenylsilyloxy)methyl)-1-[(4-methoxyphenyl)sulfonyl]-2-pyrrolidinone (preparation given) was subjected to the following transformations: i. THF, **LDA**, PhSeBr/O₃, Pyridine; ii. THF, H₂C:CHMgBr; iii. THF, LHMDS, MeI; iv. THF, LAH; v. CH₃CN, TEMPO, NaClO₂/CH₂N₂ and finally treated with hydroxylamine hydrochloride to afford II. Compds. of the invention (8 examples) had IC₅₀ ranging between 0.2 and 200 nM for the MMP-1, MMP-2, MMP-3, MMP-9 and MMP-13 enzymes.

L28 ANSWER 15 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:77482 HCAPLUS
 DOCUMENT NUMBER: 136:134955
 TITLE: Preparation of ergosterols and neuron projection regenerants
 INVENTOR(S): Kawahara, Tomio; Tachibana, Yoji
 PATENT ASSIGNEE(S): Kyorin Pharmaceutical Co., Ltd., Japan
 SOURCE: Jpn. Kokai Tokkyo Koho, 15 pp.
 CODEN: JKXXAF

DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|--|----------|-----------------|----------|
| JP 2002030096 | A2 | 20020129 | JP 2000-210316 | 20000711 |
| PRIORITY APPLN. INFO.: | | | JP 2000-210316 | 20000711 |
| OTHER SOURCE(S): | CASREACT 136:134955; MARPAT 136:134955 | | | |
| GI | | | | |



AB Steroids I (R1, R2 = H, OH, amino group, acetamide group; R3, R4 = H, Me; n = 0-2; R5, R6 = H, lower alkyl HOCH2; R7 = H, OH) are prepared by coupling reaction of phenylsulfones II (R8, R9 = H, lower alkyl, protected HOCH2; R10 = H, protected OH) with aldehydes III (R10 = H, protecting group; R3, R4 = H, Me; n = 0-2) and removal or exchange substituent of the resulting compds. at 3-position. THF solution of 35 mg II (R8 = Me; R9 = R10 = H) was reacted with 500 mg III (R3 = Me, R4 = H, R11 = tetrahydropyranyl, n = 0) in the presence of **LDA** at -70° for 30 min, deprotected with p-MeC6H4SO3H in MeOH-THF for 30 min, and treated with Na-Hg in the presence of Na2HPO4 in THF at room temperature over night to give 210 mg (24R)-ergost-22-ene-3β-ol showing good nerve cell projection regeneration activity in vitro.

L28 ANSWER 16 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2001:923164 HCAPLUS

DOCUMENT NUMBER: 136:214105

TITLE: The angiotensin converting enzyme I/D polymorphism in Russian athletes

AUTHOR(S): Nazarov, Igor B.; Woods, David R.; Montgomery, Hugh E.; Shneider, Olga V.; Kazakov, Vasiliy I.; Tomilin, Nikolai V.; Rogozkin, Viktor A.

CORPORATE SOURCE: Institute of Cytology of the Russian Academy of Sciences, St. Petersburg, 194064, Russia

SOURCE: European Journal of Human Genetics (2001), 9(10),

797-801

CODEN: EJHGEU; ISSN: 1018-4813

PUBLISHER:

Nature Publishing Group

DOCUMENT TYPE:

Journal

LANGUAGE:

English

AB The deletion (D) allele of the human ACE gene is associated with higher ACE activity than the insertion (I) allele. There is controversy as to whether the ACE genotype may be associated with elite athletic status; recent studies have identified no significant assocns. amongst those drawn from mixed sporting disciplines. However, such lack of association may reflect the mixed nature of such cohorts, given that an excess frequency of the I allele has been reported amongst elite endurance athletes, and an excess of the D allele amongst those engaged in more power-orientated sports. The authors examined this hypothesis by determining ACE I/D allele frequency amongst 217 Russian athletes (swimmers, skiers, triathletes and track-and-field participants) prospectively stratified by performance ('outstanding' or 'average'), and the duration of their event (SDA (<1 min), MDA (1 to 20 min), and LDA (>20 min): short, middle and long distance athletes resp.). ACE genotype and allele frequencies were compared to 449 controls. ACE genotype frequency amongst the whole cohort, or the outstanding athletes alone, was no different to that amongst sedentary controls. However, there was an excess of the D allele (frequency 0.72, $P=0.001$) amongst the outstanding SDA group, and an excess of the I allele (frequency 0.63, $P=0.032$) amongst the outstanding MDA group. These findings were replicated in the outstanding swimmers, with track and field SDA similarly demonstrating an excess of the D allele ($P=0.01$). There was no association found between the outstanding LDA and ACE genotype ($P=0.27$). These data not only confirm an excess of the D allele in elite SDA, and I allele in elite MDA, but also offer an explanation as to why any such association may be hard to detect amongst a heterogeneous cohort of mixed athletic ability and discipline.

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 17 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER:

2001:921430 HCAPLUS

DOCUMENT NUMBER:

136:33188

TITLE:

Evidence that the Lore-1 region specifies ethanol-induced activation in addition to sedative/hypnotic sensitivity to ethanol

AUTHOR(S):

Owens, Jeremy C.; Bennett, Beth; Johnson, Thomas E.

CORPORATE SOURCE:

Institute for Behavioral Genetics and the Department of Psychology, University of Colorado, Boulder, CO, 80309-0447, USA

SOURCE:

Alcoholism: Clinical and Experimental Research (2001), 25(11), 1551-1557

CODEN: ACRSDM; ISSN: 0145-6008

PUBLISHER:

Lippincott Williams & Wilkins

DOCUMENT TYPE:

Journal

LANGUAGE:

English

AB Low-dose ethanol-induced activation (LDA) and initial sensitivity to alc. are both predictors of alc. abuse in human populations. Our hypothesis is that one or more genes specifying hypnotic sensitivity also specify LDA. We tested this hypothesis by using congenic mice derived from the inbred long-sleep (ILS) and inbred short-sleep (ISS) strains, which carry an ILS region introgressed onto as ISS background. LDA was assessed by assigning mice randomly to receive one of five doses of ethanol ranging from 1.2 to 2.4 g/kg. On day 1, animals were injected with saline and placed in a brightly lit activity monitor for 30 min, after which they were returned to their home cages. On day 2, mice were injected with ethanol (20% w/v), their activity was monitored for a 30-min period, and LDA was determined by subtracting day 1 activity. The blood ethanol concentration of each animal was then assessed

at 30 min by retro-orbital collection of 25 µl of blood. Ethanol had a significant effect on the activity of ISS mice, but ILS mice showed no activation at any dose, similar to the activities of the outbred lines. All three congenic strains were activated at several doses. Lore-2 and Lore-5 were not ILS-like (less active than ISS) at any dose. In contrast, ISS.ILS-Lore-1 congenics (carrying an ILS-derived Lore-1 allele on the ISS background) were significantly less activated than the ISS controls at 1.8 and 2.4 g/kg of ethanol. The Lore-2 and Lore-5 congenic regions do not affect **LDA**. In contrast, the Lore-1 congenic region carries one or more genes specifying both initial hypnotic sensitivity to ethanol and **LDA**.

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 18 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2001:904178 HCAPLUS

DOCUMENT NUMBER: 136:37622

TITLE: Synthesis of caboxamidoquinazolines as caspase inhibitors

INVENTOR(S): Charrier, Jean-Damien; Brechley, Guy

PATENT ASSIGNEE(S): Vertex Pharmaceuticals Incorporated, USA

SOURCE: PCT Int. Appl., 62 pp.

CODEN: PIXXD2

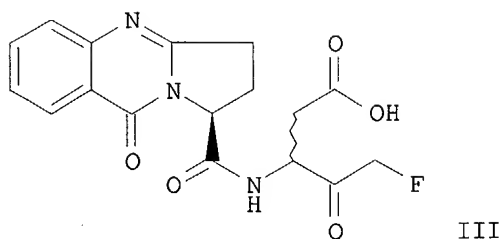
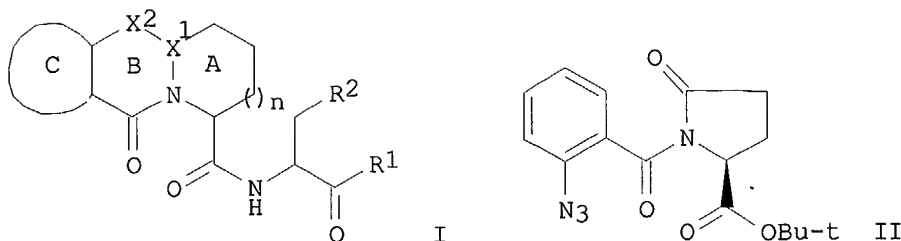
DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|--|----------|-----------------|------------|
| WO 2001094351 | A1 | 20011213 | WO 2001-US18243 | 20010605 |
| W: | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | |
| RW: | GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | |
| EP 1289993 | A1 | 20030312 | EP 2001-941972 | 20010605 |
| R: | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | |
| JP 2003535865 | T2 | 20031202 | JP 2002-501900 | 20010605 |
| US 2002045623 | A1 | 20020418 | US 2001-877832 | 20010607 |
| PRIORITY APPLN. INFO.: | | | US 2000-209929P | P 20000607 |
| | | | WO 2001-US18243 | W 20010605 |
| OTHER SOURCE(S): | MARPAT 136:37622 | | | |
| GI | | | | |



AB Title compds. I [R1 is H, CHN2, R, CH2Y; R is an aliphatic group, an aryl group, an aralkyl group, a heterocyclic group, or a heterocyclalkyl group; Y is an electroneg. leaving group; R2 is CO2H, CH2CO2H, or esters, amides or isosteres thereof; X2-X1 is NR3-CR3, C(R3)2-CR3, C(R3)2-N, N:C, CR3:N, C(R3):C, C(O)-N, or C(O)-C(R3); R3 is selected from hydrogen alkyl; Ring C is a fused aryl ring; n is 0 - 2; and each methylene carbon in Ring A is (un)substituted by :O or by one or more halo, alkyl or alkoxy] were prepared Six synthetic examples were provided. E.g., (S)-5-oxoproline tert-Bu ester was acylated with 2-azidobenzoyl chloride (THF, LDA, -78°C, 1 h) to give intermediate II. Azide II was treated with Ph3P (xylene, room temperature) which resulted in cyclization to the tricyclic intermediate. This intermediate was deprotected (TFA, room temperature) and the resulting carboxylic acid coupled to 3-amino-5-fluoro-4-hydroxypentanoic acid tert-Bu ester (THF, EDC, HOBT, DMAP, room temperature, 18 h) and the resulting alc. oxidized (CH2Cl2, Dess-Martin periodinane, room temperature, 18 h) and finally deprotected to give (CH2Cl2, TFA, room temperature, 30 min) to give III in 34% overall yield. III had $K_i = 160,500 \text{ M}^{-1}\text{s}^{-1}$ for caspase-3. Example compds. also inhibited IL-1 β secretion and showed activity in the FAS induced apoptosis assay. I are useful for treating caspase-mediated diseases.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 19 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2001:185526 HCAPLUS
 DOCUMENT NUMBER: 134:242643
 TITLE: Using quaternary ammonium salts for transdermal drug delivery
 INVENTOR(S): Fikstad, David; Ebert, Charles D.; Venkateshwaran, Srinivasan; Nilssen, Lawrence R.
 PATENT ASSIGNEE(S): Watson Pharmaceuticals, Inc., USA
 SOURCE: PCT Int. Appl., 65 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|--|------|----------|-----------------|------------|
| WO 2001017472 | A1 | 20010315 | WO 2000-US24690 | 20000908 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| EP 1217975 | A1 | 20020703 | EP 2000-961691 | 20000908 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL | | | | |
| JP 2003532629 | T2 | 20031105 | JP 2001-521266 | 20000908 |
| AU 773778 | B2 | 20040603 | AU 2000-73611 | 20000908 |
| US 2003091620 | A1 | 20030515 | US 2002-105032 | 20020321 |
| PRIORITY APPLN. INFO.: | | | | |
| | | | US 1999-153001P | P 19990908 |
| | | | US 1999-153008P | P 19990908 |
| | | | US 1999-153015P | P 19990908 |
| | | | US 2000-657080 | A 20000907 |
| | | | WO 2000-US24690 | W 20000908 |
| OTHER SOURCE(S): MARPAT 134:242643 | | | | |
| AB A transdermal drug delivery system is disclosed, which includes a polymer, a drug and an amount of a quaternary ammonium salt that is sufficient to act as a penetration enhancer. The quaternary ammonium salt may also be present in an amount sufficient to act as an irritation reducer. Further, the transdermal drug delivery system may also contain a co-enhancer, which provides a synergistic skin permeation enhancing effect when combined with the quaternary ammonium salt. A method for enhancing the transdermal delivery of a drug is also disclosed. Pressure-sensitive adhesive transdermal patches were prepared from testosterone, benzethonium chloride, acrylic/vinylpyrrolidone copolymer adhesive (DuroTak87-2888), and other ingredients. | | | | |
| IT 120-40-1, Monamid 150LWA | | | | |
| RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses) (transdermal compns. having improved penetration and decreased skin irritation containing drugs and carriers and quaternary ammonium salts) | | | | |
| REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT | | | | |

L28 ANSWER 20 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2000:612057 HCAPLUS

DOCUMENT NUMBER: 133:207816

TITLE: Preparation of aromatic amides as neuropeptide Y antagonists for treatment of eating disorders, cardiovascular diseases, and other diseases

INVENTOR(S): Carpino, Philip A.; Hammond, Maries; Hank, Richard F.

PATENT ASSIGNEE(S): Pfizer Products Inc., Japan

SOURCE: Jpn. Kokai Tokkyo Koho, 27 pp.

CODEN: JKXXAF

DOCUMENT TYPE: Patent

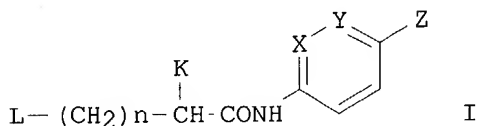
LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------|------|----------|-----------------|----------|
| JP 2000239243 | A2 | 20000905 | JP 2000-39053 | 20000217 |
| EP 1033366 | A2 | 20000906 | EP 2000-300582 | 20000126 |

EP 1033366 A3 20001227
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
 IE, SI, LT, LV, FI, RO
 US 6407120 B1 20020618 US 2000-494197 20000128
 BR 2000000486 A 20010821 BR 2000-486 20000217
 CA 2299013 AA 20000818 CA 2000-2299013 20000218
 PRIORITY APPLN. INFO.: US 1999-120593P P 19990218
 OTHER SOURCE(S): MARPAT 133:207816
 GI



AB Aromatic amides I [K = (un)substituted Ph, 2-, 3-, or 4-pyridyl; L = H, C3-8 cycloalkyl, (un)substituted Ph, 2-, 3-, or 4-pyridyl, etc.; Z = COR₃, CONR₁R₂, NR₁R₂, SO₂R₄; X, Y = CH, N; X = Y ≠ N; n = 0-3; R₁, R₂ = H, C1-6 alkyl, phenylalkyl, pyridylalkyl; NR₁R₂ may form (O- or N-containing) 4- to 8-membered ring; R₃ = C1-6 alkyl; R₄ = (cyclic) amino; when n = 0, K = L = Ph, and X = Y = C, then Z ≠ NEt₂, CO₂Et; when K = Ph, then L ≠ H] or their pharmacol. acceptable salts are prepared Treatment of Et phenylacetate with **LDA** at -78 to 0° in THF and subsequent treatment with triphenylmethylpyridinium tetrafluoroborate gave Et α-phenyl-α-(pyridin-4-yl)acetate, which was amidated with N,N-diethyl-1,4-phenylenediamine to afford N-(4-diethylaminophenyl)-2-phenyl-2-pyridin-4-yl-acetamide.

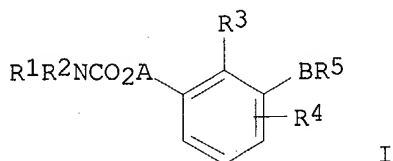
L28 ANSWER 21 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2000:441370 HCAPLUS
 DOCUMENT NUMBER: 133:58621
 TITLE: Preparation of carbamoyloxyalkylphenoxyacetates and related compounds as prostaglandin I₂ receptor agonists.
 INVENTOR(S): Lopez-Tapia, Francisco Javier; Muehldorf, Alexander Victor; O'Yang, Counde; Severance, Daniel Lee
 PATENT ASSIGNEE(S): F. Hoffmann-La Roche A.-G., Switz.
 SOURCE: Eur. Pat. Appl., 45 pp.
 CODEN: EPXXDW
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|--|------|----------|-----------------|----------|
| EP 1013639 | A1 | 20000628 | EP 1999-125027 | 19991215 |
| EP 1013639 | B1 | 20031001 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| US 6335459 | B1 | 20020101 | US 1999-456167 | 19991207 |
| AT 251125 | E | 20031015 | AT 1999-125027 | 19991215 |
| PT 1013639 | T | 20040227 | PT 1999-125027 | 19991215 |
| ES 2207108 | T3 | 20040516 | ES 1999-125027 | 19991215 |
| MX 9911894 | A | 20001031 | MX 1999-11894 | 19991216 |
| AU 9965340 | A1 | 20000706 | AU 1999-65340 | 19991217 |
| AU 735640 | B2 | 20010712 | | |
| NZ 501891 | A | 20011026 | NZ 1999-501891 | 19991217 |
| SG 90086 | A1 | 20020723 | SG 1999-6425 | 19991217 |

| | | | | |
|------------------------|----|----------|-----------------|------------|
| ZA 9907773 | A | 20000629 | ZA 1999-7773 | 19991220 |
| HR 990394 | A1 | 20000831 | HR 1999-990394 | 19991220 |
| NO 9906366 | A | 20000626 | NO 1999-6366 | 19991221 |
| JP 2000191523 | A2 | 20000711 | JP 1999-364520 | 19991222 |
| JP 3415085 | B2 | 20030609 | | |
| KR 2000048322 | A | 20000725 | KR 1999-60163 | 19991222 |
| RU 2179969 | C2 | 20020227 | RU 1999-127329 | 19991222 |
| BR 9905974 | A | 20000912 | BR 1999-5974 | 19991223 |
| CN 1266054 | A | 20000913 | CN 1999-127795 | 19991223 |
| TR 9903310 | A2 | 20001023 | TR 1999-9903310 | 19991223 |
| PRIORITY APPLN. INFO.: | | | US 1998-113446P | P 19981223 |
| | | | US 1999-151814P | P 19990830 |

OTHER SOURCE(S): MARPAT 133:58621
GI



AB Title compds. (I; R1, R2 = alkyl, aryl, aralkyl, heteroaryl, cycloalkyl, heterocyclyl; R3, R4 = H, alkyl, alkoxy, amino, halo, haloalkyl, hydroxyalkyl, NO2, aryl, aralkyl, heterocyclyl; R5 = CO2R6, tetrazolyl; R6 = H, alkyl; A = alkylene, alkenylene; B = O(CH2)m, (CH2)n; m = 1-8; n = 0-8), were prepared. Thus, tert-Bu 3-hydroxymethyl-2-methylphenoxyacetate (preparation given) in THF at -50° was treated with **LDA** and then with diphenylcarbonyl chloride in THF followed by warming room temperature to give 73% tert-Bu [3-[(diphenylcarbonyloxy)methyl]-2-methylphenoxy]acetate. This was stirred with LiOH in H2O/THF to give 95% [3-[(diphenylcarbonyloxy)methyl]-2-methylphenoxy]acetic acid. I stimulated intracellular cAMP with pEC50>4.82.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 22 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1999:685538 HCAPLUS

DOCUMENT NUMBER: 132:179017

TITLE: Serum lipid levels in patients with cerebrovascular disease. Comparison of serum Lp(a) levels with brain CT findings

AUTHOR(S): Harada, Masayuki; Kurokawa, Yoshizumi; Fukuda, Ichizo; Ohsawa, Nakaaki

CORPORATE SOURCE: First Division, Dept. of Internal Medicine, Osaka Medical College, Osaka, 569-8686, Japan

SOURCE: Bulletin of the Osaka Medical College (1998), 44(2), 63-71

CODEN: BOMCEB; ISSN: 0916-2844

PUBLISHER: Osaka Medical College

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Recently Lp(a) has been assessed as a risk factor of arteriosclerosis and its progression. A relationship between Lp(a) and coagulation/fibrinolysis is suspected, since Lp(a) closely resembles plasminogen in structure. The serum Lp(a), total-cholesterol, triglyceride and HDL-cholesterol levels were investigated in patients with cerebrovascular disease in the chronic stage by using brain CT scan findings. Simultaneously the change in plasma β -thromboglobulin (β -TG) level which is supposed to parallel platelet activation was

investigated. Lp(a) levels were increased in patients of the low-d. area (LDA) pos. group and higher in the perforating artery group than in the cortical artery group. Lp(a) levels increased, whereas total-cholesterol and triglyceride levels decreased with age. We conclude the changes of serum Lp(a) levels are independent of those of other lipids, and strongly correlate to plasma β -thromboglobulin levels.

This suggests a direct influence of serum Lp(a) on coagulation/fibrinolysis and especially on platelet activation.

REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 23 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1999:464290 HCAPLUS

DOCUMENT NUMBER: 131:116147

TITLE: Preparation of naphthylmethylcycloalkafuranones and related compounds as modulators of subtype 1 metabotropic glutamate receptors.

INVENTOR(S): Stolle, Andreas; Antonicek, Horst-Peter; Lensky, Stephen; Voerste, Arnd; Muller, Thomas; Baumgarten, Jorg; Von Dem Bruch, Karsten; Muller, Gerhard; Stropp, Udo; Horvath, Ervin; De Vry, Jean-Marie Viktor; Schreiber, Rudy

PATENT ASSIGNEE(S): Bayer Aktiengesellschaft, Germany

SOURCE: PCT Int. Appl., 126 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: German

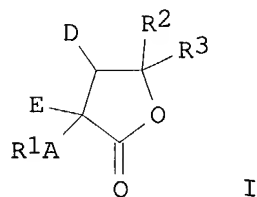
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|------------------|------------|
| WO 9936418 | A1 | 19990722 | WO 1999-EP31 | 19990107 |
| W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| DE 19801636 | A1 | 19990722 | DE 1998-19801636 | 19980117 |
| AU 9925157 | A1 | 19990802 | AU 1999-25157 | 19990107 |
| EP 1047686 | A1 | 20001102 | EP 1999-904744 | 19990107 |
| R: DE, ES, FR, GB, IT | | | | |
| JP 2002509146 | T2 | 20020326 | JP 2000-540134 | 19990107 |
| US 6376539 | B1 | 20020423 | US 2000-600395 | 20000714 |
| PRIORITY APPLN. INFO.: | | | DE 1998-19801636 | A 19980117 |
| | | | WO 1999-EP31 | W 19990107 |

OTHER SOURCE(S): MARPAT 131:116147

GI



AB Title compds. [I; A = CH₂, CO, CR₄OH, (CH₂)_aCHR₅; a = 0-4; R₄ = H, alkyl; R₅ = Ph, alkylene, alkenylene, alkynylene; R₁ = H, cycloalkyl, heterocyclyl; R₂, R₃ = H, alkyl; DE = CH₂CH₂, (substituted) (CH₂)₃, (CH₂)₄, CH₂CH:CHCH₂, etc.], were prepared for preventing and/or treating diseases caused by the hyper- or hypofunction of the glutamatergic system, especially cerebral ischemia, cranial/cerebral trauma, pain or CNS-mediated cramps (no data). Thus, cis-8-oxabicyclo[4.3.0]nonane-9-one was treated with LDA in THF at -78°; PhCH₂Br was added followed by 16 h stirring at room temperature to give 38.2% cis-1-benzyl-8-oxabicyclo[4.3.0]nonane-9-one.

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 24 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1999:48694 HCAPLUS

DOCUMENT NUMBER: 130:124898

TITLE: Preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivatives as MEK inhibitors
INVENTOR(S): Barrett, Stephen Douglas; Bridges, Alexander James; Cody, Donna Reynolds; Doherty, Annette Marian; Dudley, David Thomas; Saltiel, Alan Robert; Schroeder, Mel Conrad; Tecle, Haile

PATENT ASSIGNEE(S): Warner-Lambert Company, USA

SOURCE: PCT Int. Appl., 67 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

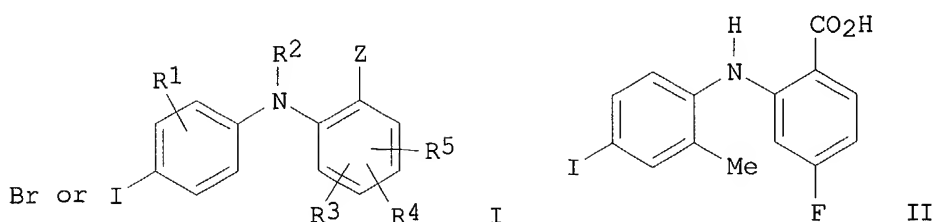
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|-------------|
| WO 9901421 | A1 | 19990114 | WO 1998-US13105 | 19980624 |
| W: AL, AU, BA, BB, BG, BR, CA, CN, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| AU 9882626 | A1 | 19990125 | AU 1998-82626 | 19980624 |
| AU 756586 | B2 | 20030116 | | |
| EP 993437 | A1 | 20000419 | EP 1998-932829 | 19980624 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| BR 9810385 | A | 20000905 | BR 1998-10385 | 19980624 |
| JP 2002509536 | T2 | 20020326 | JP 1999-507227 | 19980624 |
| NZ 501277 | A | 20021220 | NZ 1998-501277 | 19980624 |
| ZA 9805726 | A | 19990127 | ZA 1998-5726 | 19980630 |
| MX 9910556 | A | 20000430 | MX 1999-10556 | 19991116 |
| US 6310060 | B1 | 20011030 | US 2000-462319 | 20000105 |
| US 6506798 | B1 | 20030114 | US 2001-889084 | 20010711 |
| US 2002022647 | A1 | 20020221 | US 2001-931596 | 20010816 |
| US 6492363 | B2 | 20021210 | | |
| US 2003149015 | A1 | 20030807 | US 2002-315654 | 20021210 |
| PRIORITY APPLN. INFO.: | | | US 1997-51433P | P 19970701 |
| | | | WO 1998-US13105 | W 19980624 |
| | | | WO 1999-US30418 | W 19991221 |
| | | | US 2000-462319 | A2 20000105 |
| | | | US 2001-931596 | A3 20010816 |

OTHER SOURCE(S): MARPAT 130:124898
GI



AB The title compds. [I; R1 = H, OH, C1-8 alkyl, etc.; R2 = H; R3-R5 = H, OH, halo, etc.; Z = COOR7, tetrazolyl, CONR6R7, etc.; R6, R7 = H, C1-8 alkyl, C2-8 alkenyl, etc.], which are potent inhibitors of MEK and, as such, are effective in treating cancer and other proliferative diseases such as inflammation, psoriasis and restenosis, as well as stroke, heart failure, and immunodeficiency disorders, were prepared and formulated. Thus, treatment of 2-amino-5-iodotoluene in THF with **LDA** in THF/heptane/ethylbenzene solution followed by addition of 2,4-difluorobenzoic acid in THF afforded II which showed IC₅₀ of 0.019 μ M against MEK in vitro.

REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 25 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1998:457266 HCAPLUS

DOCUMENT NUMBER: 129:76517

TITLE: Anticonvulsant and anxiolytic lactam and thiolactam derivatives

INVENTOR(S): Covey, Douglas F.; Reddy, P. Amruta; Ferrendelli, James A.

PATENT ASSIGNEE(S): Washington University, USA

SOURCE: U.S., 19 pp.

CODEN: USXXAM

DOCUMENT TYPE: Patent

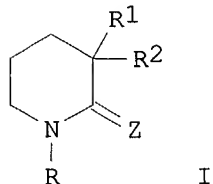
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|--------|-----------|-----------------|----------|
| US 5776959 | A | 19980707 | US 1995-462102 | 19950605 |
| US 6066666 | A | 20000523 | US 1998-45211 | 19980320 |
| PRIORITY APPLN. INFO.: | | | US 1995-462102 | 19950605 |
| OTHER SOURCE(S): | MARPAT | 129:76517 | | |

GI



AB Title compds. I [Z = O, S; R-R2 = H, (un)substituted alkyl, CH₂Ph], which have anticonvulsant and anxiolytic activity, enhance GABA-induced chloride currents at the GABA receptor/ionophore complex. Thus,

1-benzyl-2-piperidinone was treated with PhCH₂Br and LDA, followed by debenzylation with Li-NH₃ to give 3-benzyl-2-piperidinone which had an anticonvulsant ED₅₀ of 85 mg/kg in the epntetrazole test and 42 mg/kg in the maximum electroshock test.

REFERENCE COUNT: 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 26 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1997:658297 HCAPLUS

DOCUMENT NUMBER: 127:316329

TITLE: Relationship between redistribution rate (RD rate) of 123I-IMP SPECT and prognosis by Barthel index in cerebral infarction

AUTHOR(S): Fukumitsu, Nobuyoshi; Ogi, Shigeyuki; Uchiyama, Masayuki; Mori, Yutaka; Kawakami, Kenji; Miyano, Satoshi; Mashio, Kiyoshi; Takehara, Itaru

CORPORATE SOURCE: Dep. Radiol., Jikei Univ. Sch. Med., Tokyo, 105, Japan
SOURCE: Nippon Igaku Hoshasen Gakkai Zasshi (1997), 57(11), 660-667

CODEN: NHGZAR; ISSN: 0048-0428

PUBLISHER: Nippon Igaku Hoshasen Gakkai

DOCUMENT TYPE: Journal

LANGUAGE: Japanese

AB A comparative study of RD rate and the Barthel index was performed in 26 patients who had cerebral infarction. On 123I-IMP SPECT, the RD rate was calculated as follows, RD rate = (I-II)/I + 100(%). I = (B - A)/B, where A is the mean count of the low d. area (LDA) on brain CT on the early image and B is the mean count of the opposite portion of LDA on the early image. II = (B' - A')/B', where A' is the mean count of the LDA on the delayed image and B' is the mean count of the opposite portion of the LDA on the delayed image. The Δ Barthel index (Δ B.I.) was defined as follows: Δ B.I. = B.I. (post-rehabilitation) - B.I. (pre-rehabilitation). In the group with B.I. (pre-rehabilitation) < 85, the RD rate and Δ B.I. were well correlated. In the group with B.I. (pre-rehabilitation) \geq 85, the RD rate and Δ B.I. were not correlated. This result suggests that the RD rate might be useful in predicting prognosis and selecting the principle of therapy.

L28 ANSWER 27 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1997:618069 HCAPLUS

DOCUMENT NUMBER: 127:293126

TITLE: Pyrrolidinone hydroxamic acid derivatives for use in the treatment of diseases related to connective tissue degradation

INVENTOR(S): Jacobsen, E. Jon

PATENT ASSIGNEE(S): Pharmacia & Upjohn Co., USA; Jacobsen, E. Jon

SOURCE: PCT Int. Appl., 207 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

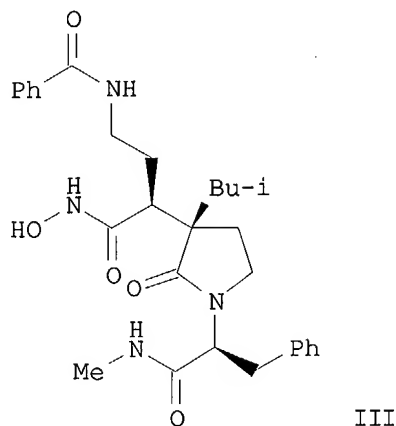
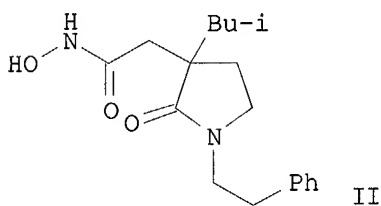
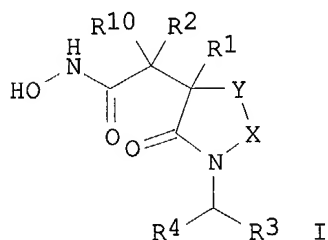
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------|--|----------|-----------------|----------|
| WO 9732846 | A1 | 19970912 | WO 1997-US2568 | 19970303 |
| W: | AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | |
| RW: | GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, | | | |

GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN,
ML, MR, NE, SN, TD, TG

| | | | | |
|--|----|-------------------|------------------|------------|
| TW 448172 | B | 20010801 | TW 1997-86102076 | 19970221 |
| CA 2244903 | AA | 19970912 | CA 1997-2244903 | 19970303 |
| AU 9720525 | A1 | 19970922 | AU 1997-20525 | 19970303 |
| AU 707180 | B2 | 19990701 | | |
| EP 898562 | A1 | 19990303 | EP 1997-908674 | 19970303 |
| EP 898562 | B1 | 20030122 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| CN 1210517 | A | 19990310 | CN 1997-192171 | 19970303 |
| BR 9707947 | A | 19990727 | BR 1997-7947 | 19970303 |
| NZ 330922 | A | 20000128 | NZ 1997-330922 | 19970303 |
| JP 2000506163 | T2 | 20000523 | JP 1997-531784 | 19970303 |
| RU 2168497 | C2 | 20010610 | RU 1998-118372 | 19970303 |
| AT 231490 | E | 20030215 | AT 1997-908674 | 19970303 |
| ES 2191823 | T3 | 20030916 | ES 1997-908674 | 19970303 |
| ZA 9701902 | A | 19980907 | ZA 1997-1902 | 19970305 |
| NO 9804112 | A | 19981106 | NO 1998-4112 | 19980907 |
| PRIORITY APPLN. INFO.: | | | US 1996-13098P | P 19960308 |
| | | | WO 1997-US2568 | W 19970303 |
| OTHER SOURCE(S): | | MARPAT 127:293126 | | |
| GI | | | | |



AB The invention provides novel hydroxamic acid derivs. I and their pharmaceutically acceptable salts [wherein X = CH₂, NR₅, CO; Y = CH₂, NR₅; provided that Y = CH₂ when X = NR₅; R₁ = H, alkyl, (CH₂)_i-Ar, (CH₂)_iOR₅, (CH₂)_i-Het, etc.; R₂ = H, alkyl, (CH₂)_jOR₅, NHR₅, (CH₂)_jNR₆R₇, etc; R₃ = H, alkyl, (CH₂)_j-Ar, (CH₂)_j-Het, (CH₂)_j-cycloalkyl, CONHR₅; R₄ = H, CONHR₅, CONR₆R₇, other derivs. of CONH₂, etc.; R₅ = H, alkyl, (CH₂)_j-Ar, (CH₂)_j-Ar-Ar, (CH₂)_j-Ar-(CH₂)_j-Ar, (CH₂)_j-Het, (CH₂)_j-cycloalkyl; R₆, R₇ =

H, alkyl, (CH₂)_j-Ar, Q; or NR₆R₇ = (optionally alkyl-substituted) azetidiny, pyrrolidinyl, piperazinyl, piperidinyl, or morpholinyl; R₁₀ = H, OH, OR₅, NHR₅, (CH₂)_jOR₅; Ar = (un)substituted Ph; Het = 5- or 6-membered N/O/S heterocycle; Q = saturated 5- or 6-membered N/O/S heterocycle; i = 1-6, j = 0-4]. I inhibit various enzymes from the matrix metalloproteinase family, including collagenase, stromelysin, and gelatinase, and are useful for the treatment of matrix metallo-endoproteinase diseases such as osteoarthritis, rheumatoid arthritis, septic arthritis, osteopenias such as osteoporosis, tumor metastasis (invasion and growth), periodontitis, gingivitis, corneal, dermal, and gastric ulceration, and other diseases related to connective tissue degradation. For instance, 1-(2-phenylethyl)-2-pyrrolidinone underwent a sequence of lithiation with LDA and C-alkylation with iso-BuI (99%), a second alkylation with BrCH₂COBu-tert (68%), saponification with CF₃CO₂H (92%), and hydroxamidation with NH₂OH.HCl using EDC and HOBT (31%), to give title compound II. The title compound III inhibited matrix metalloproteinases in vitro with K_i (μM) as follows: stromelysin 0.0105, gelatinase 0.00106, and collagenase 0.00069.

IT **513-38-2**, 1-Iodo-2-methylpropane

RL: RCT (Reactant); RACT (Reactant or reagent)

(starting material; preparation of pyrrolidinone hydroxamic acid derivs. for treatment of connective tissue degradation diseases)

L28 ANSWER 28 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1997:478545 HCAPLUS

DOCUMENT NUMBER: 127:131574

TITLE: Regulation by interleukin-1β of formation of a line of delimiting astrocytes following prenatal trauma to the brain of the mouse

AUTHOR(S): Scripser, Jori L.; Ko, Jane; Kow, Kelvin; Arimura, Akira; Ide, Charles F.

CORPORATE SOURCE: Department of Cell and Molecular Biology, Center for Bioenvironmental Research and U.S.-Japan Biomedical Laboratories, Neuroscience Training Program, Tulane University, New Orleans, LA, 70118, USA

SOURCE: Experimental Neurology (1997), 145(2, Pt. 1), 329-341
CODEN: EXNEAC; ISSN: 0014-4886

PUBLISHER: Academic

DOCUMENT TYPE: Journal

LANGUAGE: English

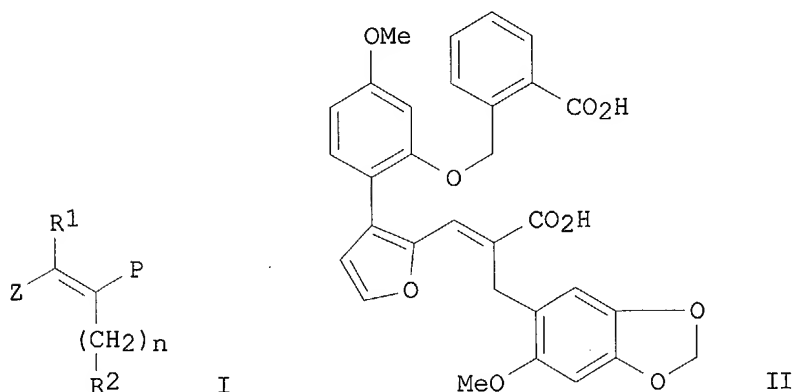
AB The regulation of perinatal glia limitans (GL) reformation by interleukin-1β (IL-1β) following prenatal neural trauma in the mouse was studied in lesioned fetal mice by immunocytochem. and computer-assisted image anal. for presence and distribution of astrocytes and IL-1β immunoreactivity (ir). Astrocytes stained with anti-glial fibrillary acidic protein (GFAP) were observed as a line of delimiting astrocytes (LDA) near the lesion edge on Postnatal Day 0 (P0, 2 days postlesion). At P6, a new and complete GL composed of GFAP-pos. astrocytes was continuous with that of adjacent undamaged tissue. The new GL was located in the same area at P6 as was the LDA at P0, suggesting that the LDA is the precursor structure to a reformed GL. Astrocytes comprising the new GL were pos. for anti-IL-1β. The IL-1 receptor antagonist (IL-1ra), administered acutely into the lesion, produced a significantly decreased optical d. of IL-1β-ir at the LDA at P0 compared to animals that received injections of vehicle, human recombinant IL-1β, or a combination injection of IL-1ra + IL-1β. Furthermore, although GFAP-stained cells appeared at the lesion site, an organized LDA was not visible at P0 in IL-1ra-treated animals. Vehicle-, IL-1β-, and combination-injected animals showed a robust LDA at the lesion site at P0. These data suggest that upregulation of IL-1β in astrocytes and interaction of IL-1β with the neural IL-1 receptor are important for reconstruction of the GL following prenatal lesion in the murine brain.

L28 ANSWER 29 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1997:231072 HCAPLUS
 DOCUMENT NUMBER: 126:212034
 TITLE: Furan and thiophene derivatives and their preparation and use as endothelin receptor antagonists.
 INVENTOR(S): Elliott, John Duncan; Gao, Aiming; Xiang, Jia-ning
 PATENT ASSIGNEE(S): Smithkline Beecham Corporation, USA; Elliott, John Duncan; Gao, Aiming; Xiang, Jia-Ning
 SOURCE: PCT Int. Appl., 34 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|--|------|----------|-----------------|------------|
| WO 9704769 | A1 | 19970213 | WO 1996-US12583 | 19960802 |
| W: JP, US | | | | |
| RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |
| EP 841916 | A1 | 19980520 | EP 1996-926840 | 19960802 |
| EP 841916 | B1 | 20030702 | | |
| R: BE, CH, DE, ES, FR, GB, IT, LI, NL | | | | |
| JP 11511132 | T2 | 19990928 | JP 1996-507889 | 19960802 |
| ES 2197243 | T3 | 20040101 | ES 1996-926840 | 19960802 |
| US 6017952 | A | 20000125 | US 1998-737851 | 19980202 |
| US 6051599 | A | 20000418 | US 1999-399434 | 19990920 |
| PRIORITY APPLN. INFO.: | | | | |
| | | | US 1995-1793P | P 19950802 |
| | | | US 1996-10983P | P 19960201 |
| | | | WO 1996-US12583 | W 19960802 |

OTHER SOURCE(S): MARPAT 126:212034
 GI



AB Novel furans and thiophene derivs. I, pharmaceutical compns. containing I, and their use as endothelin receptor antagonists (no data) are described [wherein Z = (un)substituted 2- or 4-phenyl-3-furyl or -thienyl, 3-phenyl-2-furyl or -thienyl; P = CO₂H or certain esters or amides, tetrazol-5-yl; R₁ = H, alkyl; R₂ = aryl, alkyl, acyl, (un)substituted cycloalkyl; n = 0-6]. Three synthetic examples and three formulations are given. For instance, 3-bromofuran was lithiated with **LDA** and formylated with DMF to give 41% 3-bromofuran-2-carboxaldehyde. This underwent Pd(PPh₃)₄-catalyzed arylation by 2-(methoxymethoxy)-4-methoxyphenylboronic acid (100%), and condensation with di-Et 2-(2-methoxy-4,5-methylenedioxybenzyl)malonate (36%), to give a

3-(furan-2-yl)-2-propenoate derivative intermediate. Deprotection of the methoxymethyl ether group (41%), etherification of the resulting phenol with Me 2-(bromomethyl)benzoate and NaH (97%), and basic hydrolysis of the ester functions (47%), gave title compound II.

L28 ANSWER 30 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1996:410431 HCAPLUS

DOCUMENT NUMBER: 125:86627

TITLE: Preparation of spiroazabicyclic compounds for treatment of psychosis, anxiety, and intellectual impairment.

INVENTOR(S): Balestra, Michael; Gordon, John Charles; Griffith, Ronald Conrad; Murray, Robert John

PATENT ASSIGNEE(S): Astra Aktiebolag, Swed.

SOURCE: PCT Int. Appl., 21 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

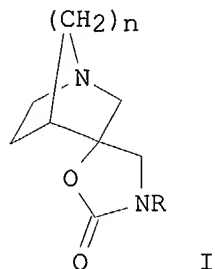
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|------------------|------------|
| WO 9606098 | A1 | 19960229 | WO 1995-SE937 | 19950822 |
| W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM | | | | |
| RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| CA 2196995 | AA | 19960229 | CA 1995-2196995 | 19950822 |
| AU 9534018 | A1 | 19960314 | AU 1995-34018 | 19950822 |
| AU 690735 | B2 | 19980430 | | |
| EP 777671 | A1 | 19970611 | EP 1995-930755 | 19950822 |
| EP 777671 | B1 | 20000426 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE | | | | |
| BR 9508751 | A | 19970812 | BR 1995-8751 | 19950822 |
| CN 1159808 | A | 19970917 | CN 1995-195518 | 19950822 |
| CN 1056846 | B | 20000927 | | |
| HU 77352 | A2 | 19980330 | HU 1997-1965 | 19950822 |
| JP 10504561 | T2 | 19980506 | JP 1995-507995 | 19950822 |
| RU 2148058 | C1 | 20000427 | RU 1997-104165 | 19950822 |
| AT 192157 | E | 20000515 | AT 1995-930755 | 19950822 |
| ES 2145922 | T3 | 20000716 | ES 1995-930755 | 19950822 |
| PT 777671 | T | 20000831 | PT 1995-930755 | 19950822 |
| EE 3399 | B1 | 20010416 | EE 1997-39 | 19950822 |
| SK 282366 | B6 | 20020107 | SK 1997-216 | 19950822 |
| CZ 289512 | B6 | 20020213 | CZ 1997-392 | 19950822 |
| PL 183933 | B1 | 20020830 | PL 1995-318760 | 19950822 |
| IL 115039 | A1 | 20010826 | IL 1995-115039 | 19950823 |
| ZA 9507122 | A | 19960418 | ZA 1995-7122 | 19950824 |
| TW 397837 | B | 20000711 | TW 1995-84108836 | 19950824 |
| US 5902814 | A | 19990511 | US 1995-525575 | 19950918 |
| NO 9700800 | A | 19970221 | NO 1997-800 | 19970221 |
| FI 9700762 | A | 19970224 | FI 1997-762 | 19970224 |
| HK 1010370 | A1 | 20000728 | HK 1998-110995 | 19980926 |
| US 6051581 | A | 20000418 | US 1998-188099 | 19981109 |
| CN 1284505 | A | 20010221 | CN 1999-123574 | 19991108 |
| CN 1099419 | B | 20030122 | | |
| GR 3033878 | T3 | 20001130 | GR 2000-401563 | 20000704 |
| PRIORITY APPLN. INFO.: | | | GB 1994-17084 | A 19940824 |
| | | | GB 1995-4627 | A 19950308 |

OTHER SOURCE(S):
GI

MARPAT 125:86627



AB Title compds. (I; R = H, Me; n = 1, 2), were prepared as agonists of $\alpha 7$ nAChR (nicotinic acetylcholine) receptors (no data). Thus, Me₃COAc and then quinuclidine-3-one were added to **LDA** in THF at -78° and the mixture was allowed to warm to 0° over 1 h to give tert-Bu 2-(3-hydroxy-1-azabicyclo[2.2.2]oct-3-yl)acetate. This was converted to the hydrazide, which in aqueous HCl was treated with aqueous NaNO₂ at 0° to give spiro[1-azabicyclo[2.2.2]octane-3,5'-oxazolidine]-2'-one hydrochloride.

L28 ANSWER 31 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1995:397628 HCAPLUS

DOCUMENT NUMBER: 122:188083

TITLE: Enantiomerically enriched α -methyl amino acids.
Use of an acyclic, chiral alanine-derived dianion with a high diastereofacial bias

AUTHOR(S): Berkowitz, David B.; Smith, Marianne K.

CORPORATE SOURCE: Department of Chemistry, University of Nebraska
-Lincoln, Lincoln, NE, 68588-0304, USA

SOURCE: Journal of Organic Chemistry (1995), 60(5), 1233-8
CODEN: JOCEAH; ISSN: 0022-3263

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Hindered esters derived from N-benzoylalanine and the following chiral alcs. have been synthesized: (-)-isopinocampheol, (-)-trans-2-phenylcyclohexanol, and (-)-8-phenylmenthol. Sequential treatment of these esters with **LDA** (1.2 equiv) and n-butyllithium (2.4 equiv) at -78° in THF generates the corresponding chiral dianions. Alkylation of each of these with benzyl bromide reveals that only the (-)-8-phenylmenthyl auxiliary confers a high diastereofacial bias upon its derivative dianion. In fact, that dianion (6) consistently displays diastereomeric ratios in the range of 89:11 to 94:6 for alkylations with a spectrum of nine alkyl halides. If one recrystn. step is included, a single diastereomeric product may be obtained, as is demonstrated for the benzylation of 6. Of particular note, the alkylation with 3,4-bis[(tert-butyldimethylsilyl)oxy]benzyl bromide (94:6 diastereomeric ratio, 72% yield) constitutes a formal synthesis of the clin. important antihypertensive (S)- α -methyl-DOPA (Aldomet), in enantiomerically enriched form. In all cases studied, yields are markedly improved, yet diastereoselectivities unchanged, by the addition of 10% HMPA to the reaction milieu. The (-)-8-phenylmenthol chiral auxiliary is conveniently recovered via ester cleavage with KO₂/18-crown-6, following alkylation. Complete deprotection affords enantiomerically enriched (S)- α -Me

amino acids, in all cases examined, indicating that dianion 6 displays a substantial bias in favor of si face alkylation. This sense of diastereoselection is consistent with a chain-extended, internal chelate model for the reactive conformation of the dianion.

IT 513-38-2, Isobutyl iodide

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of enantiomerically enriched Me amino acids via alkylation of an acyclic chiral alanine-derived dianion)

L28 ANSWER 32 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1994:295820 HCAPLUS

DOCUMENT NUMBER: 120:295820

TITLE: RFLP haplotyping and mutation analysis of the phenylalanine hydroxylase gene in Dutch phenylketonuria families

AUTHOR(S): Meijer, Henk; Jongbloed, Roselie J. E.; Hekking, M.; Spaapen, Leo J. M.; Geraedts, Joep P. M.

CORPORATE SOURCE: Dep. Clin. Genet. Mol. Cell Biol., Univ. Limburg, Maastricht, 6229 GR, Neth.

SOURCE: Human Genetics (1993), 92(6), 588-92

CODEN: HUGEDQ; ISSN: 0340-6717

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Restriction fragment length polymorphism haplotyping of mutated and normal phenylalanine hydroxylase (PAH) alleles in 49 Dutch phenylketonuria (PKU) families was performed. All mutant PAH chromosomes identified by haplotyping (n = 98) were screened for eight of the most predominant mutations. Compound heterozygosity was proven in 40 kindreds. Homozygosity was found for the IVS12nt1 mutation in 5 families, and for the R158Q and IVS10nt546 mutations in one family each. All patients from these families suffer from severe PKU, providing addnl. proof that these mutations are deleterious for the PAH gene. Genotypical heterogeneity was evident for mutant haplotype 1 (n = 27) carrying the mutations R261Q (n = 12), E280K (n = 4), P281L (n = 1) and unknown (n = 10), and likewise for mutant haplotype 4 (n = 30) carrying the mutations R158Q (n = 13), Y414C (n = 1) and unknown (n = 16). Mutant haplotype 3 (n = 20), in tight association with mutation IVS12nt1, appeared to be in strong linkage disequil. (LDE) with its normal counterpart allele (n = 4). Mutant haplotype 6 (n = 4), in tight association with the IVS10nt546 mutation, showed moderate LDE with its counterpart allele (n = 1). The distribution of the mutant PAH haplotypes 1, 3 and 4 among the Dutch PKU population resembles that in other Northern and Western European countries, but it is striking that mutant haplotype 2 and its associated mutation R408W is nearly absent in The Netherlands, in strong contrast to its neighboring countries.

L28 ANSWER 33 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1993:539175 HCAPLUS

DOCUMENT NUMBER: 119:139175

TITLE: Stereoselective synthesis of novel centrally active benzomorphan-type tricycles with 2-phenylethylamine substructure

AUTHOR(S): Wuensch, Bernhard; Hoefner, Georg; Bauschke, Gerd

CORPORATE SOURCE: Inst. Pharm. Lebensmittelchemie, Univ. Muenchen, Munich, 8000, Germany

SOURCE: Archiv der Pharmazie (Weinheim, Germany) (1993), 326(2), 101-13

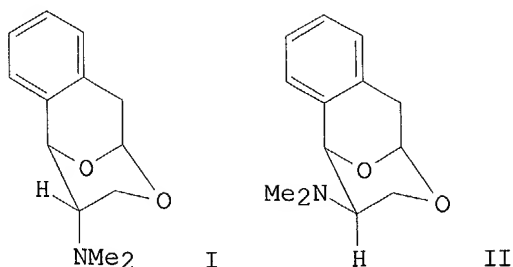
CODEN: ARPMAS; ISSN: 0365-6233

DOCUMENT TYPE: Journal

LANGUAGE: German

OTHER SOURCE(S): CASREACT 119:139175

GI



AB Addn of the **LDA**-deprotonated Et dimethylglycinate to homophthalaldehyde monoacetal gave the β -hydroxy ster I which was cyclized after reduction to give the racemic 2,6-epoxy-3-benzoxocin-5-aminens (\pm)-I and (\pm)-II. The key intermediates for the synthesis of (\pm)-I and (\pm)-II in enantiomerically pure form were hydroxyacetal precursors; the stereoselective synthesis of which was given. The enantiomeric amines (R,R,S)-I and (R,S,S)-II were prepared starting form (R)-serine. Symptoms typical for sedation are observed after application of both enantiomers of I and II to mice. In the acetic acid writhing test (mouse) (S,S,R)-I, (S,R,R)-II, (R,S,S)-II exhibit strong analgesic effects with ED50-values in the range of the ED50-value of tramadol-HCl.

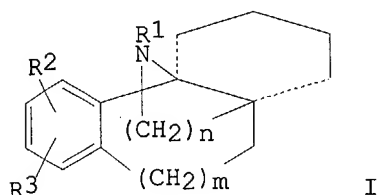
L28 ANSWER 34 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 1993:81351 HCAPLUS
 DOCUMENT NUMBER: 118:81351
 TITLE: Direct synthesis of Boc protected (D,L)-amino acids from Boc-glycine
 AUTHOR(S): De Nicola, A.; Einhorn, J.; Luche, J. L.
 CORPORATE SOURCE: Lab. Etud. Dyn. Struct. Sel., Univ. J. Fourier, Grenoble, 38041, Fr.
 SOURCE: Tetrahedron Letters (1992), 33(43), 6461-4
 CODEN: TELEAY; ISSN: 0040-4039
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 OTHER SOURCE(S): CASREACT 118:81351

AB Boc-Gly-OH (Boc = Me₃CO₂C) is easily deprotonated by lithium diisopropylamide (**LDA**), yielding a trianion which is trapped with an electrophile to give access to Boc DL-amino acids. Thus, the treatment of Boc-Gly-OH with **LDA** gave the trianion, which was treated in situ with MeI and then quenched with water to give DL-BocNHCHMeCO₂H. In the reaction of Boc-Gly-OH with Br(CH₂)₃Cl, Boc-DL-Pro-OH was obtained as the major product. When D₂O was used as the electrophile, deuterated product BocNHCHDCO₂H was obtained.

IT **513-38-2**, Isobutyl iodide
 RL: RCT (Reactant); RACT (Reactant or reagent)
 (alkylation by, of (tert-butoxycarbonyl)glycine trianion)

L28 ANSWER 35 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 1992:128661 HCAPLUS
 DOCUMENT NUMBER: 116:128661
 TITLE: Preparation of tetracyclic amines as cerebrovascular agents
 INVENTOR(S): Malone, Thomas C.
 PATENT ASSIGNEE(S): Warner-Lambert Co., USA
 SOURCE: U.S., 18 pp. Division of U.S. Ser. No. 565,306.
 CODEN: USXXAM
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|--|------|-------------------|-----------------|----------|
| US 5070093 | A | 19911203 | US 1991-677029 | 19910328 |
| US 5109136 | A | 19920428 | US 1990-565306 | 19900809 |
| WO 9202219 | A1 | 19920220 | WO 1991-US5853 | 19910808 |
| W: AU, CA, JP | | | | |
| RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE | | | | |
| AU 9186346 | A1 | 19920302 | AU 1991-86346 | 19910808 |
| US 5245028 | A | 19930914 | US 1991-753479 | 19910903 |
| PRIORITY APPLN. INFO.: | | | US 1990-565306 | 19900809 |
| | | | US 1991-677029 | 19910328 |
| | | | WO 1991-US5853 | 19910808 |
| OTHER SOURCE(S): | | MARPAT 116:128661 | | |
| GI | | | | |



AB Title compds. I [R1 = H, C1-4 alkyl, C2-4 alkenyl, C2-4 alkynyl, aryl-C1-4 alkyl, cyclopropyl-C1-4 alkyl; R2, R3 = H, C1-4 alkyl, OH, C1-4 alkoxy, halo, NH2, (di)C1-4 alkylamino; m = 0-2; n = 2-4] were prepared as cerebrovascular agents (no data). Thus, 3',4'-dihydrospiro[cyclopentane-1,1'(2'H)-naphthalen]-2'-one (preparation from 2-tetralone and Br(CH2)4Br given) was cyanomethylated by MeCN in the presence of **LDA**. The product was reduced by Raney Ni and the aminoethyl derivative was treated with ClCO2CH2CCl3 to give the carbonate. Thus was cyclized by HOAc/H2SO4 to give 2,2,2-trichloroethyl (±)-2,3,4,5-tetrahydro-3a,9b-butano-1H-benz[g]indole-1-carboxylate. Decarboxylation by Zn dust in MeOH/HOAc gave title compound I (R1-R3 = H, m = 1; n = 2).HCl. Several I bound to phencyclidine receptors with affinities of < 10 μM.

L28 ANSWER 36 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1989:213338 HCAPLUS

DOCUMENT NUMBER: 110:213338

TITLE: Preparation, testing, and formulation of 1-phenyl-2-methyl-2-propyl 2-aminoalkanoates as central nervous system agents

INVENTOR(S): Hoegberg, Thomas; Hogberg, Thomas; Lindberg, Ulf
Henrik Anders; Ulff, Carl Bengt Johan; Oegren, Sven
Ove

PATENT ASSIGNEE(S): Astra AB, Swed.

SOURCE: Eur. Pat. Appl., 19 pp.

CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

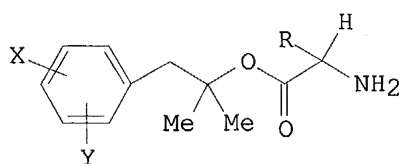
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------|------|----------|-----------------|----------|
| EP 293351 | A2 | 19881130 | EP 1988-850178 | 19880524 |
| EP 293351 | A3 | 19890222 | | |
| EP 293351 | B1 | 19920325 | | |
| R: ES, GR | | | | |

WO 8809327 A1 19881201 WO 1988-SE271 19880524
W: AT, AU, BB, BG, BR, CH, DE, DK, FI, GB, HU, JP, KP, KR, LK, LU,
MC, MG, MW, NL, NO, RO, SD, SE, SU, US
RW: AT, BE, BJ, CF, CG, CH, CM, DE, FR, GA, GB, IT, LU, ML, MR, NL,
SE, SN, TD, TG
AU 8819403 A1 19881221 AU 1988-19403 19880524
EP 362264 A1 19900411 EP 1988-905026 19880524
R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE
JP 02503559 T2 19901025 JP 1988-504745 19880524
AT 74122 E 19920415 AT 1988-850178 19880524
ES 2039290 T3 19930916 ES 1988-850178 19880524
CA 1307793 A1 19920922 CA 1988-567778 19880526
US 4990534 A 19910205 US 1989-305728 19890124
PRIORITY APPLN. INFO.: SE 1987-2228 19870527
SE 1987-4372 19871109
EP 1988-850178 19880524
WO 1988-SE271 19880524

OTHER SOURCE(S): MARPAT 110:213338
GI

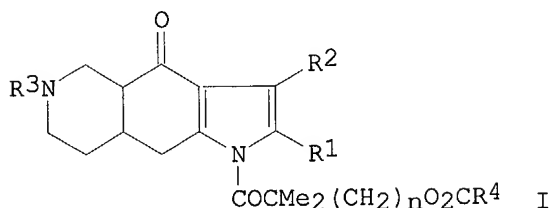


AB The title compds. [I; R = C2-5 (unsatd.) alkyl; X, Y = H, halo, CF₃; provided that both X and Y ≠ H, and excluding the racemate in which X = 4-Cl, Y = H, and R = Me₂CH], useful for treating mental disorders, were prepared Bis(chlorodimethylsilyl)ethane in CH₂Cl₂ was added dropwise to 4-ClC₆H₄CH₂CMe₂OCOCH₂NH₂ and Et₃N in CH₂Cl₂ and the mixture was stirred 1.5 h at room temperature The crude stabase adduct in THF was added to LDA and TMEDA in THF/hexane at -20°. The mixture was stirred 1.5 h and EtI was added at -10°. The mixture was stirred 2.5 h at -10° and the product in Et₂O was hydrolyzed with 1N HCl to give 4-ClC₆H₄CH₂CMe₂OCOCH(NH₂)Et. I potentiated oxotremorine-induced tremors in rats at 2.5-20 mg/kg i.p.

L28 ANSWER 37 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1988:406431 HCAPLUS
DOCUMENT NUMBER: 109:6431
TITLE: Preparation of acylpyrroloisoquinolinones as long-acting antipsychotics
INVENTOR(S): Berger, Leo; Olson, Gary Lee
PATENT ASSIGNEE(S): Hoffmann-La Roche, F., und Co. A.-G., Switz.
SOURCE: Eur. Pat. Appl., 44 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| EP 246529 | A2 | 19871125 | EP 1987-106817 | 19870511 |
| EP 246529 | A3 | 19890419 | | |
| R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE | | | | |
| US 4732902 | A | 19880322 | US 1986-866532 | 19860523 |
| DK 8702556 | A | 19871124 | DK 1987-2556 | 19870520 |

| | | | | |
|------------------------|-------------------|----------|----------------|----------|
| ZA 8703637 | A | 19880127 | ZA 1987-3637 | 19870520 |
| FI 8702233 | A | 19871124 | FI 1987-2233 | 19870521 |
| NO 8702157 | A | 19871124 | NO 1987-2157 | 19870522 |
| AU 8773315 | A1 | 19871126 | AU 1987-73315 | 19870522 |
| HU 43601 | A2 | 19871130 | HU 1987-2289 | 19870522 |
| HU 197744 | B | 19890529 | | |
| JP 62283971 | A2 | 19871209 | JP 1987-126840 | 19870523 |
| PRIORITY APPLN. INFO.: | | | US 1986-866532 | 19860523 |
| OTHER SOURCE(S): | CASREACT 109:6431 | | | |
| GI | | | | |



AB The title compds. (I; R1, R2 = H, C1-4 alkyl, cycloalkyl, alkenyl; R1R2 = C3-6 alkylene; R3 = H, alkyl, hydroxyalkyl, phenylhydroxyalkyl, halophenylhydroxyalkyl, alkenyl, alkynyl, thienylalkyl, furylalkyl, etc.; R4 = alkyl, n = 2,3) were prepared as antipsychotics. (±)-3-Ethyl-2,6-dimethyl-1,4a,5,6,7,8,8a,9-octahydro-4a,8a-trans-4H pyrrolo[2,3g]isoquinolin-4-one was added to a -40 to -50° solution of LDA in THF and the mixture was stirred at -20 to -30° for 30 min. 2,2-Dimethyl-4-[(1-oxodecyl)oxy]butanoyl chloride in THF was added over 30 min to give (±)-III. The latter exhibited an ED50 of 3.6 mg/kg i.v. in rats in the pole climb avoidance test. A long-acting depot parenteral formulation was prepared from 250 mg (±)-III and 10 mL sesame oil.

L28 ANSWER 38 OF 38 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1988:38319 HCAPLUS

DOCUMENT NUMBER: 108:38319

TITLE: Asymmetric alkylations of glycine derivatives using optically active formylcamphors

AUTHOR(S): Suzuki, Kojiro; Hirami, Yasumichi; Taniai, Michi; Mohri, Tomoyo; Goda, Chie; Fujiyama, Ryoji; Kiyooka, Syunichi

CORPORATE SOURCE: Fac. Sci., Kochi Univ., Kochi, 780, Japan

SOURCE: Nippon Kagaku Kaishi (1987), (2), 186-90

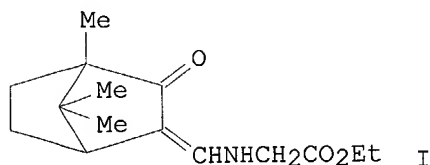
CODEN: NKAKB8; ISSN: 0369-4577

DOCUMENT TYPE: Journal

LANGUAGE: Japanese

OTHER SOURCE(S): CASREACT 108:38319

GI



AB Treatment of 3-(hydroxymethylene)camphor, the enol of 3-formylcamphor, with Et glycinate afforded aminomethylene derivative I. Alkylations of I with Me iodide and benzyl chloride in the presence of **LDA** afforded L-amino acids in low asym. yields, e.g., Ala (9.2% e.e.) and Phe (4.3% e.e.). N-Methyl-D-alanine (43.3% e.e.) and N-methyl-D-phenylalanine (26.5% e.e.) were obtained by the same alkylations when Et N-methylglycinate was used instead of Et glycinate. Thus, pronounced effect of N-substituent of glycine was observed exo-3-Formyl-3-methylcamphor was prepared and allowed to react with Et glycinate to give the Schiff base. The Schiff base would be expected to activate the methylene group of glycine moiety and to increase the enantioselectivity by the 3-Me group of the camphor moiety. The alkylations of the Schiff base with Me iodide, benzyl chloride and iso-Bu iodide gave L-Ala (70.2% e.e.), D-Phe (84.7% e.e.) and L-Leu (71.6% e.e.), resp.

IT **513-38-2**, Isobutyl iodide

RL: RCT (Reactant); RACT (Reactant or reagent)
(asym. alkylation by, of glycine Schiff base)

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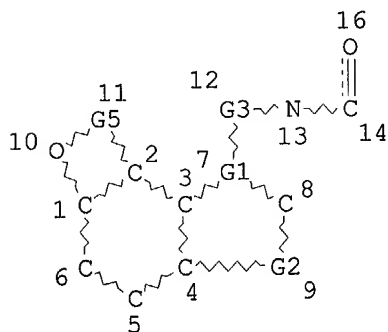
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 FILE 'HCAPLUS' ENTERED AT 10:56:05 ON 27 OCT 2004
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 PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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FILE COVERS 1907 - 27 Oct 2004 VOL 141 ISS 18
 FILE LAST UPDATED: 26 Oct 2004 (20041026/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d stat que 128
 L6 STR



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 VAR G2=C/N/O/S
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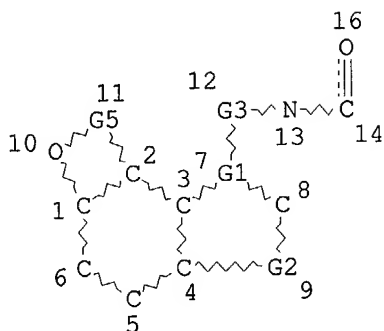
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 RING(S) ARE ISOLATED OR EMBEDDED
 NUMBER OF NODES IS 15

STEREO ATTRIBUTES: NONE

L7 92 SEA FILE=REGISTRY SSS FUL L6
 L8 37 SEA FILE=HCAPLUS ABB=ON PLU=ON L7
 L28 0 SEA FILE=HCAPLUS ABB=ON PLU=ON L8 AND (SHAMPOO OR COSMETIC)

=> □

=> d stat que
 L2 77 SEA FILE=REGISTRY ABB=ON PLU=ON DIETHANOLAMIDE?
 L6 STR



VAR G1=C/N
 VAR G2=C/N/O/S
 REP G3=(1-4) C
 REP G5=(2-4) A
 NODE ATTRIBUTES:
 DEFAULT MLEVEL IS ATOM
 DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
 RING(S) ARE ISOLATED OR EMBEDDED
 NUMBER OF NODES IS 15

STEREO ATTRIBUTES: NONE

L7 92 SEA FILE=REGISTRY SSS FUL L6
 L8 37 SEA FILE=HCAPLUS ABB=ON PLU=ON L7
 L9 SEL PLU=ON L7 1- CHEM : 96 TERMS
 L10 38 SEA FILE=HCAPLUS ABB=ON PLU=ON L9
 L13 6557 SEA FILE=HCAPLUS ABB=ON PLU=ON L2 OR ?ETHANOLAMID?
 L14 1 SEA FILE=HCAPLUS ABB=ON PLU=ON L10 AND L13
 L29 36 SEA FILE=HCAPLUS ABB=ON PLU=ON L8 NOT L14

=>
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=> d ibib abs hitstr 129 1-36

L29 ANSWER 1 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2004:610036 HCAPLUS
 DOCUMENT NUMBER: 141:145717
 TITLE: Sedative non-benzodiazepine formulations
 INVENTOR(S): O'Toole, Edel; Fogarty, Siobhan
 PATENT ASSIGNEE(S): Biovail Laboratories Inc., Barbados
 SOURCE: PCT Int. Appl., 67 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------|------|----------|-----------------|----------|
| WO 2004062564 | A2 | 20040729 | WO 2004-IB18 | 20040108 |
| WO 2004062564 | A3 | 20040910 | | |

W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ,

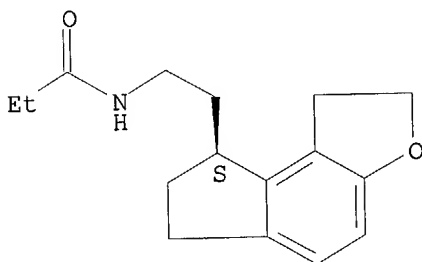
KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN,
 MW, MX, MX, MZ
 US 2003165566 A1 20030904 US 2003-338876 20030109
 PRIORITY APPLN. INFO.: US 2003-338876 A 20030109
 US 2002-346613P P 20020110

AB The invention provides for an enhanced absorption pharmaceutical composition comprising a plurality of microparticles, each microparticle comprising at least one sedative non-benzodiazepine, at least one spheronization aid and at least one solubility enhancer. The microparticles of the invention are further incorporated into an oral fast-dispersing dosage form.

IT 196597-26-9, TAK-375
 RL: PEP (Physical, engineering or chemical process); PYP (Physical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
 (sedative non-benzodiazepine formulations)

RN 196597-26-9 HCAPLUS
 CN Propanamide, N-[2-[(8S)-1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L29 ANSWER 2 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2004:197432 HCAPLUS
 DOCUMENT NUMBER: 140:296697
 TITLE: TAK-375: treatment of insomnia treatment of circadian rhythm disorders melatonin MT1/MT2 agonist
 AUTHOR(S): Chilman-Blair, K.; Castaner, J.; Silvestre, J. S.; Bayes, M.
 CORPORATE SOURCE: Prous Science, Barcelona, 08080, Spain
 SOURCE: Drugs of the Future (2003), 28(10), 950-958
 CODEN: DRFUD4; ISSN: 0377-8282
 PUBLISHER: Prous Science
 DOCUMENT TYPE: Journal; General Review
 LANGUAGE: English

AB A review. Melatonin is a neurohormone produced in the pineal gland that is involved in the regulation of circadian rhythm function. It works through activation of its intrinsic receptors found in the suprachiasmatic nucleus (SCN) within the hypothalamus. Melatonin synthesis is under direct neural control from SCN firing. The sleep/wake cycle is a circadian rhythm controlled by this neural complex. Problems in the functioning of this system can therefore lead to sleep disorders. While melatonin itself has been shown to be effective in the treatment of sleep disorders, problems due to its ubiquitous action in the brain have limited its use for this indication. TAK-375 is a potent melatonin receptor agonist, specific for the ML1 receptor subtype known to be intricately involved in circadian rhythm function. TAK-375 has been heralded as an exciting new drug candidate for the treatment of patients with insomnia and circadian rhythm dysfunction. Phase III trials are currently under way to test the drug's viability for use in patients with sleep disorders.

IT 196597-26-9P, TAK-375

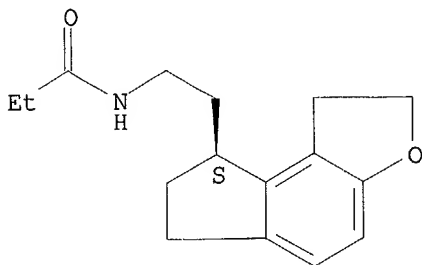
RL: ADV (Adverse effect, including toxicity); DMA (Drug mechanism of action); PAC (Pharmacological activity); PKT (Pharmacokinetics); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(melatonin MT1/MT2 agonist TAK-375 treatment of patients with insomnia and circadian rhythm disorders)

RN 196597-26-9 HCAPLUS

CN Propanamide, N-[2-[(8S)-1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 3 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2004:78471 HCAPLUS

DOCUMENT NUMBER: 140:264809

TITLE: Molecular pharmacology of the ovine melatonin receptor: comparison with recombinant human MT1 and MT2 receptors

AUTHOR(S): Mailliet, Francois; Audinot, Valerie; Malpoux, Benoit; Bonnaud, Anne; Delagrangue, Philippe; Migaud, Martine; Barrett, Perry; Viaud-Massuad, Marie-Claude; Lesieur, Daniel; Lefoulon, Francois; Renard, Pierre; Boutin, Jean A.

CORPORATE SOURCE: Physiologie de la Reproduction et des Comportements, UMR INRA-CNRS-Universite de Tours, Nouzilly, 37380, Fr.

SOURCE: Biochemical Pharmacology (2004), 67(4), 667-677
CODEN: BCPA6; ISSN: 0006-2952

PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The variations of the pharmacol. properties of melatonin receptors between different mammalian species in transfected cell lines have been poorly investigated. In the present study, melatonin analogs have been used to characterize the pharmacol. of the recombinant ovine melatonin receptor (oMT1) expressed in CHO cell lines and the native oMT1 from the pars tuberalis (PT). Studies with selective ligands on native and transfected oMT1 showed similar properties for binding affinities [$r^2(\text{PT}/\text{CHO}) = 0.85$]. The affinities and the functional activities of these ligands were compared with the human receptors (hMT1 or hMT2) expressed in CHO cells as well. The oMT1 and hMT1 receptors had similar pharmacol. profiles ($r^2=0.82$). Nevertheless, some of the selective compds. at the human receptor presented a reduced affinity at the ovine receptor. Furthermore, some compds. showed marked different functional activities at oMT1 vs. hMT1 receptors. Our findings demonstrated differences in the pharmacol. properties of melatonin receptors in ovine and human species.

IT 251360-39-1

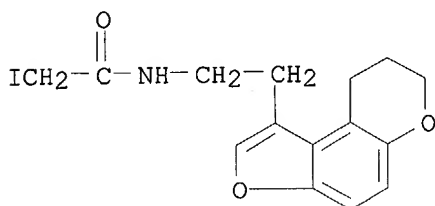
RL: BSU (Biological study, unclassified); PKT (Pharmacokinetics); BIOL

(Biological study)

(receptor ligand; mol. pharmacol. of ovine melatonin receptor in comparison with recombinant human MT1 and MT2 receptors)

RN 251360-39-1 HCAPLUS

CN Acetamide, N-[2-(8,9-dihydro-7H-furo[3,2-f][1]benzopyran-1-yl)ethyl]-2-iodo- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 4 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:897579 HCAPLUS

DOCUMENT NUMBER: 140:296592

TITLE: Recent progress of hypnotic drug therapy

AUTHOR(S): Nakajima, Toru; Sugano, Michi

CORPORATE SOURCE: School of Medicine, Kyorin University, Japan

SOURCE: Gendai Iryo (2003), 35(10), 2439-2446

CODEN: GEIRDK; ISSN: 0533-7259

PUBLISHER: Gendai Iryosha

DOCUMENT TYPE: Journal; General Review

LANGUAGE: Japanese

AB A review. The history and characteristic of hypnotic drugs including w1 selectivity, the influence of hypnotic drugs on the different sleeping stages, the metabolism of hypnotic drugs, and recent development of hypnotic drugs such as TAK-375 etc. is reviewed.

IT 196597-26-9, TAK-375

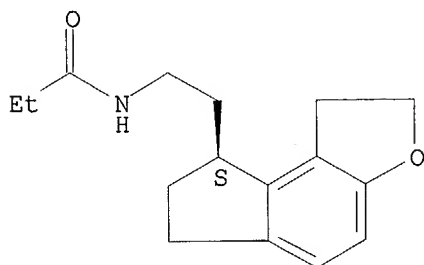
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(recent progress of hypnotic drug therapy)

RN 196597-26-9 HCAPLUS

CN Propanamide, N-[2-[(8S)-1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L29 ANSWER 5 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:606476 HCAPLUS

DOCUMENT NUMBER: 139:285646

TITLE: A Novel and Selective 5-HT2 Receptor Agonist with

Ocular Hypotensive Activity: (S)-(+)-1-(2-Aminopropyl)-8,9-dihydropyrano[3,2-e]indole

AUTHOR(S): May, Jesse A.; Chen, Hwang-Hsing; Rusinko, Andrew; Lynch, Vincent M.; Sharif, Najam A.; McLaughlin, Marsha A.

CORPORATE SOURCE: Medicinal Chemistry Molecular Pharmacology, and In Vivo Pharmacology Departments, Ophthalmic Products Research, Alcon Research, Ltd., Fort Worth, TX, 76134, USA

SOURCE: Journal of Medicinal Chemistry (2003), 46(19), 4188-4195
CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

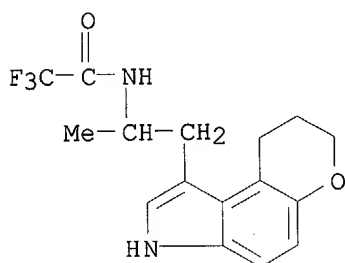
OTHER SOURCE(S): CASREACT 139:285646

AB Serotonin 5-HT₂ receptor agonists have recently been shown to be effective in lowering intraocular pressure in nonhuman primates and represent a potential new class of antiglaucoma agents. As part of an effort to identify new selective agonists at this receptor, we have found that (S)-(+)-1-(2-aminopropyl)-8,9-dihydropyrano[3,2-e]indole (AL-37350A) has high affinity and selectivity (>1000-fold) for the 5-HT₂ receptor relative to other 5-HT receptors. More specifically, AL-37350A is a potent agonist at the 5-HT_{2A} receptor (EC₅₀ = 28.6 nM, E_{max} = 103%) that is comparable to serotonin. Evaluation of AL-37350A in conscious ocular hypertensive cynomolgus monkeys showed this compound to be efficacious in reducing intraocular pressure (13.1 mmHg, -37%). Thus, AL-37350A is a potent full agonist with selectivity for the 5-HT₂ receptor and is anticipated to serve as a useful tool in exploring the role of the 5-HT₂ receptor and its effector system in controlling intraocular pressure.

IT **608135-03-1P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and structure-activity relationship of (S)-(+)-1-(2-aminopropyl)-8,9-dihydropyrano[3,2-e]indole as a novel and selective 5-HT₂ receptor agonist with ocular hypotensive activity)

RN 608135-03-1 HCAPLUS

CN Acetamide, 2,2,2-trifluoro-N-[1-methyl-2-(3,7,8,9-tetrahydropyrano[3,2-e]indol-1-yl)ethyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 6 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:570816 HCAPLUS

DOCUMENT NUMBER: 139:138735

TITLE: Sedative non-benzodiazepine formulations

INVENTOR(S): O'Toole, Edel; Fogarty, Siobhan

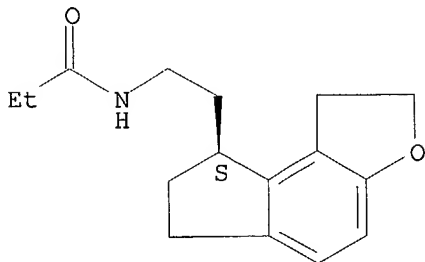
PATENT ASSIGNEE(S): Biovail Laboratories Inc., Barbados

SOURCE: PCT Int. Appl., 59 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|--|----------|-----------------|------------|
| WO 2003059349 | A1 | 20030724 | WO 2003-IE1 | 20030109 |
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| EP 1469848 | A1 | 20041027 | EP 2003-729537 | 20030109 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | | |
| PRIORITY APPLN. INFO.: | | | US 2002-346613P | P 20020110 |
| | | | WO 2003-IE1 | W 20030109 |
| AB | The invention provides for an enhanced absorption pharmaceutical composition comprising a plurality of microparticles, each microparticle comprising at least one sedative non-benzodiazepine, at least one spheronisation aid, and at least one solubility enhancer. The microparticles of the invention are further incorporated into an oral fast-dispersing dosage form. For example, microparticles were prepared containing zolpidem tartrate 15%, Gelucire 50/13 35%, and distilled monoglyceride (Myvaplex) 50%. Microparticles obtained were then coated for taste masking with a coating solution containing a 60:30:10 ratio of Eudragit NE30D, talc, and Methocel. The coated microparticles were used for preparation of tablets. | | | |
| IT | 196597-26-9, TAK 375 RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (preparation of microparticles for enhanced oral bioavailability of non-benzodiazepine sedatives) | | | |
| RN | 196597-26-9 HCAPLUS | | | |
| CN | Propanamide, N-[2-[(8S)-1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl]ethyl]- (9CI) (CA INDEX NAME) | | | |

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 7 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2003:467787 HCAPLUS
 DOCUMENT NUMBER: 139:358927

TITLE: New selective ligands of human cloned melatonin MT1 and MT2 receptors

AUTHOR(S): Audinot, Valerie; Mailliet, Francois; Lahaye-Brasseur, Chantal; Bonnaud, Anne; Le Gall, Aude; Amosse, Christophe; Dromaint, Sandra; Rodriguez, Marianne; Nagel, Nadine; Galizzi, Jean-Pierre; Malpaux, Benoit; Guillaumet, Gerald; Lesieur, Daniel; Lefoulon, Francois; Renard, Pierre; Delagrang, Philippe; Boutin, Jean A.

CORPORATE SOURCE: Division de Pharmacologie Moleculaire et Cellulaire, Institut de Recherches Servier, Croissy-sur-Seine, 78290, Fr.

SOURCE: Naunyn-Schmiedeberg's Archives of Pharmacology (2003), 367(6), 553-561
CODEN: NSAPCC; ISSN: 0028-1298

PUBLISHER: Springer-Verlag

DOCUMENT TYPE: Journal

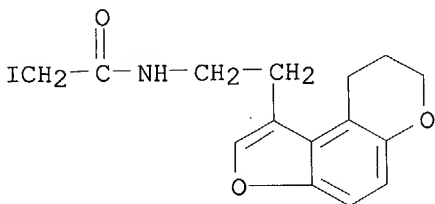
LANGUAGE: English

AB Melatonin has a key role in the circadian rhythm relay to periphery organs. Melatonin exerts its multiple roles mainly through two seven transmembrane domain, G-coupled receptors, namely MT1 or MT2 receptors. A pharmacol. characterization of these human cloned melatonin hMT1 and hMT2 receptors stably expressed in HEK-293 or CHO cells is presented using a 2-[125I]-iodo-melatonin binding assay and a [35S]-GTPγS functional assay. Both reference compds. and new chemical diverse ligands were evaluated. Binding affinities at each receptor were found to be comparable on either HEK-293 or CHO cell membranes. Novel non-selective or selective hMT1 and hMT2 ligands are described. The [35S]-GTPγS functional assay was used to define the functional activity of these compds. which included partial, full agonist and/or antagonist activity. None of the compds. acted as an inverse agonist. The authors report new types of selective antagonists, such as S 25567 and S 26131 for MT1 and S 24601 for MT2. These studies brought other new mol. tools such as the selective MT1 agonist, S 24268, as well as the non-selective antagonist, S 22153. Finally, the authors also discovered S 25150, the most potent melatonin receptor agonist, so far reported in the literature.

IT 251360-39-1
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(binding activity and functional activity of selective ligands of human cloned melatonin MT1 and MT2 receptors)

RN 251360-39-1 HCAPLUS

CN Acetamide, N-[2-(8,9-dihydro-7H-furo[3,2-f][1]benzopyran-1-yl)ethyl]-2-iodo- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 8 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN

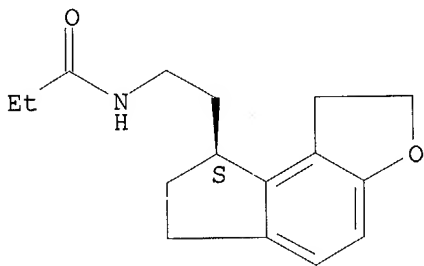
ACCESSION NUMBER: 2003:285637 HCAPLUS

DOCUMENT NUMBER: 140:8509

TITLE: Chiral technology in medicine product formulation

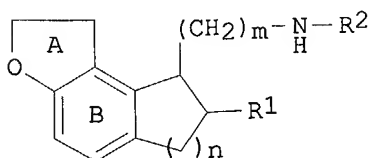
AUTHOR(S): Yamano, Toru
 CORPORATE SOURCE: Dep. of Drugs, Takeda Chemical Industries, Ltd., Japan
 SOURCE: Fain Kemikaru (2003), 32(5), 9-15
 CODEN: FNKMAU; ISSN: 0913-6150
 PUBLISHER: Shi Emu Shi Shuppan
 DOCUMENT TYPE: Journal; General Review
 LANGUAGE: Japanese
 AB A review on chiral technol., e.g. optical resolution and asym. synthesis, in production of chiral drugs, covering synthesis of intermediates for production of an anti-diabetic agent (a 2,4-oxazolidinedione derivative) and a hypnotic agent (TAK-375) as examples. Asym. hydrogenation, asym. Reformatsky reaction, and optical resolution by using lipase are also discussed.
 IT **196597-26-9P**, TAK 375
 RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (chiral technol. in drug preparation)
 RN 196597-26-9 HCAPLUS
 CN Propanamide, N-[2-[(8S)-1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L29 ANSWER 9 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2002:685086 HCAPLUS
 DOCUMENT NUMBER: 137:184576
 TITLE: Indane derivatives enzymic resolution
 INVENTOR(S): Tarui, Naoki; Okawa, Shigeki; Kawada, Mitsuru
 PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan
 SOURCE: Jpn. Kokai Tokkyo Koho, 13 pp.
 CODEN: JKXXAF
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|--|----------|-----------------|----------|
| JP 2002253297 | A2 | 20020910 | JP 2001-52056 | 20010227 |
| PRIORITY APPLN. INFO.: | | | JP 2001-52056 | 20010227 |
| OTHER SOURCE(S): | CASREACT 137:184576; MARPAT 137:184576 | | | |
| GI | | | | |



I

AB Optically active indane derivs. (I: R1 = H, (un)substituted hydrocarbon; R2 = H or (un)substituted acyl; A = (un)substituted five- to seven-member O-containing heterocyclic ring, etc.; B = (un)substituted benzene ring; n = 1-4) are manufactured from racemic reactants by asym. hydrolysis with bacteria such as Bacillus and Corynebacterium. I are useful for control of sleep disorder.

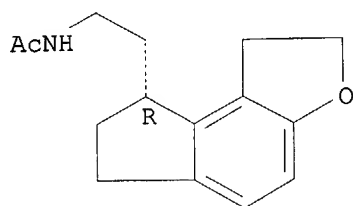
IT **431063-33-1P**

RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(indane derivs. enzymic resolution)

RN 431063-33-1 HCAPLUS

CN Acetamide, N-[2-[(8R)-1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl]ethyl]-
(9CI) (CA INDEX NAME)

Absolute stereochemistry.

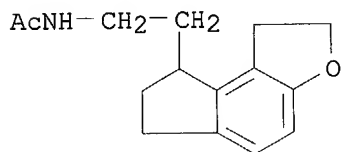


IT **196597-16-7**

RL: RCT (Reactant); RACT (Reactant or reagent)
(indane derivs. enzymic resolution)

RN 196597-16-7 HCAPLUS

CN Acetamide, N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]-
(9CI) (CA INDEX NAME)



L29 ANSWER 10 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:608507 HCAPLUS

DOCUMENT NUMBER: 137:185374

TITLE: Synthesis of a Novel Series of Tricyclic Indan Derivatives as Melatonin Receptor Agonists

AUTHOR(S): Uchikawa, Osamu; Fukatsu, Kohji; Tokunoh, Ryosuke; Kawada, Mitsuru; Matsumoto, Kiyoharu; Imai, Yumi; Hinuma, Shuji; Kato, Koki; Nishikawa, Hisao; Hirai, Keisuke; Miyamoto, Masaomi; Ohkawa, Shigenori

CORPORATE SOURCE: Pharmaceutical Research Division, Takeda Chemical Industries Ltd., Osaka, 532-8686, Japan

SOURCE: Journal of Medicinal Chemistry (2002), 45(19), 4222-4239

CODEN: JMCMAR; ISSN: 0022-2623

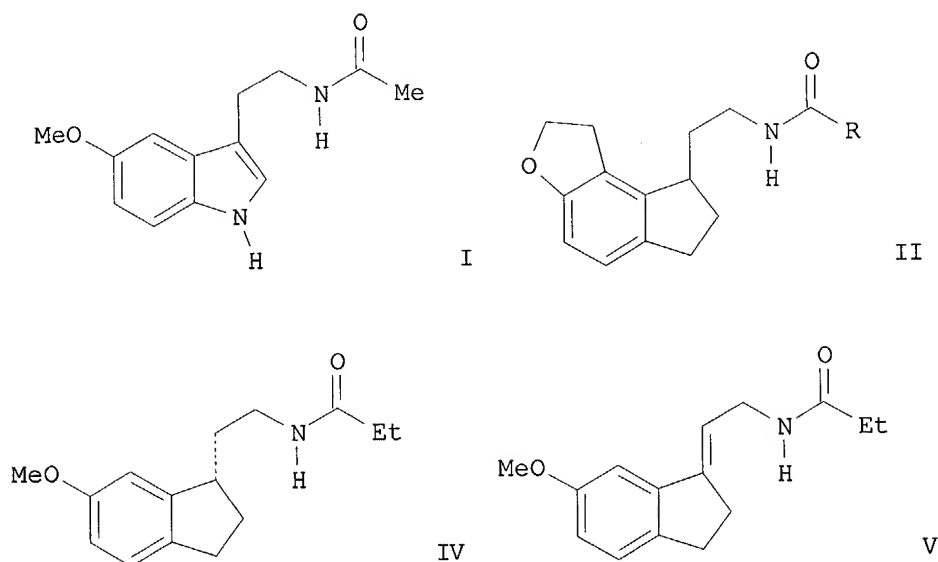
PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 137:185374

GI



AB A novel series of tricyclic indan derivs. were prepared as potential therapeutic agents for sleep disorders and evaluated for their binding affinity to melatonin receptors. Previously, a conformation of the methoxy group of melatonin (I) resulting in optimal binding of the MT1 receptor had been proposed. To fix the methoxy group in an active conformation, we decided to synthesize conformationally restricted tricyclic indan analogs with the oxygen atom in the 6-position incorporated into a furan, 1,3-dioxane, oxazole, pyran, morpholine, or 1,4-dioxane ring system. Among these compds., indeno[5,4-b]furan analogs II (R = Me, Et, n-Pr) were found to be the most potent and selective MT1 receptor ligands and to have superior metabolic stability. The optimization of substituents led to (S)-II [R = Et (III)], which showed very strong affinity for human MT1 ($K_i = 0.014$ nM), but no significant affinity for hamster MT3 ($K_i = 2600$ nM) or other neurotransmitter receptors. The pharmacol. effects of III were studied in exptl. animals, and it was found that a dose of 0.1 mg/kg, po promoted a sleep in freely moving cats, as demonstrated by a decrease in wakefulness and increases in slow wave sleep and rapid eye movement sleep, which lasted for 6 h after administration. I (1 mg/kg, po) also had a sleep-promoting effect, though it lasted only 2 h. A new chiral method for the synthesis of III starting from IV, which was prepared from V employing asym. hydrogenation with the (S)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl-Ru complex, was developed. III (TAK-375) is currently in clin. trials for the treatment of insomnia and circadian rhythm disorders.

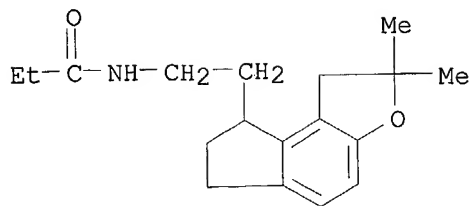
IT 196597-45-2P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)

(preparation and melatonin receptor affinity of (dimethylfuranoindenyl)ethyl propionamide via bromination of (methoxyindenyl)ethyl propionamide followed by demethylation, O-alkylation, Claisen rearrangement, cyclization, and hydrogenation)

RN 196597-45-2 HCAPLUS

CN Propanamide, N-[2-(1,6,7,8-tetrahydro-2,2-dimethyl-2H-indeno[5,4-b]furan-8-yl)ethyl]- (9CI) (CA INDEX NAME)



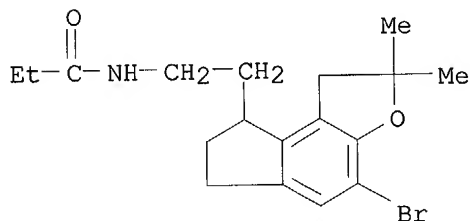
IT 196597-44-1P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation and melatonin receptor affinity of (dimethylfuranoindenyl)ethyl propionamide via bromination of (methoxyindenyl)ethyl propionamide followed by demethylation, O-alkylation, Claisen rearrangement, cyclization, and hydrogenation)

RN 196597-44-1 HCAPLUS

CN Propanamide, N-[2-(4-bromo-1,6,7,8-tetrahydro-2,2-dimethyl-2H-indeno[5,4-b]furan-8-yl)ethyl]- (9CI) (CA INDEX NAME)



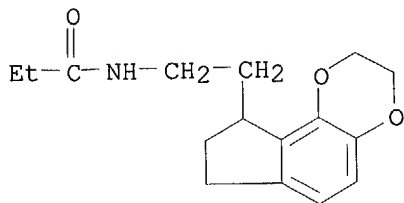
IT 196597-36-1P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)

(preparation and melatonin receptor affinity of (dioxanoindenyl)ethyl propionamide via alkylation of (dihydroxyindenyl)ethyl propionamide with dibromoethane)

RN 196597-36-1 HCAPLUS

CN Propanamide, N-[2-(2,3,8,9-tetrahydro-7H-indeno[4,5-b]-1,4-dioxin-9-yl)ethyl]- (9CI) (CA INDEX NAME)



IT 196597-34-9P

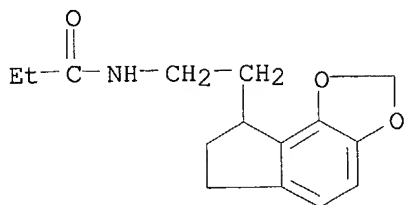
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)

(preparation and melatonin receptor affinity of (dioxolanoindenyl)ethyl propionamide via Horner-Emmons reaction of dimethoxyindanone with di-Et cyanomethylphosphonate followed by hydrogenation, amidation, demethylation, and cyclization)

RN 196597-34-9 HCAPLUS

CN Propanamide, N-[2-(7,8-dihydro-6H-indeno[4,5-d]-1,3-dioxol-8-yl)ethyl]-

(9CI) (CA INDEX NAME)

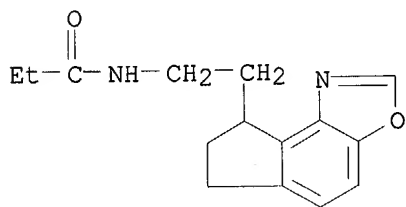


IT 196597-39-4P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and melatonin receptor affinity of (oxazoloindenyl)ethyl propionamide via nitration of methoxyindanone followed by Horner-Emmons reaction with di-Et cyanomethylphosphonate, hydrogenation, amidation, demethylation, and cyclization)

RN 196597-39-4 HCAPLUS

CN Propanamide, N-[2-(7,8-dihydro-6H-indeno[4,5-d]oxazol-8-yl)ethyl]- (9CI)
(CA INDEX NAME)

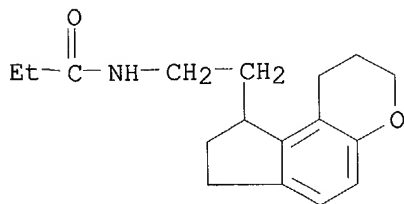


IT 196597-43-0P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and melatonin receptor affinity of (pyranoindenyl)ethyl propionamide via propargylation of (bromohydroxyindenyl)ethyl propionamide followed by thermal cyclization and hydrogenation)

RN 196597-43-0 HCAPLUS

CN Propanamide, N-[2-(1,2,3,7,8,9-hexahydrocyclopenta[f][1]benzopyran-9-yl)ethyl]- (9CI) (CA INDEX NAME)

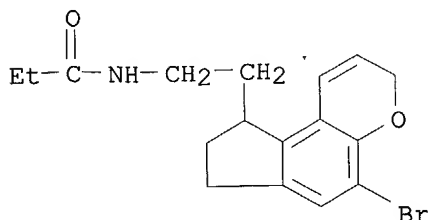


IT 196597-41-8P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and melatonin receptor affinity of (pyranoindenyl)ethyl propionamide via propargylation of (bromohydroxyindenyl)ethyl propionamide followed by thermal cyclization and hydrogenation)

RN 196597-41-8 HCAPLUS

CN Propanamide, N-[2-(5-bromo-3,7,8,9-tetrahydrocyclopenta[f][1]benzopyran-9-yl)ethyl]- (9CI) (CA INDEX NAME)

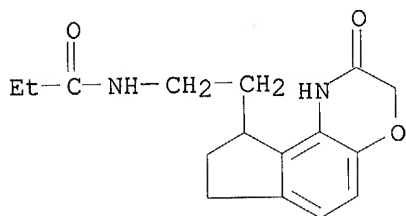


IT 196597-49-6P 196597-51-0P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and melatonin receptor affinity of oxazinoindanes via nitration of hydroxyindanone followed by O-alkylation with bromoacetate, hydrogenation, cyclization, Horner-Emmons reaction, reduction, and amidation)

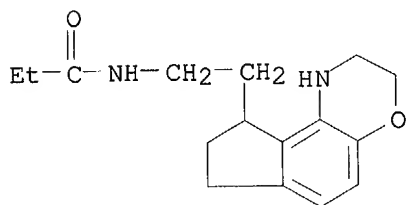
RN 196597-49-6 HCAPLUS

CN Propanamide, N-[2-(1,2,3,7,8,9-hexahydro-2-oxoindeno[5,4-b][1,4]oxazin-9-yl)ethyl]- (9CI) (CA INDEX NAME)



RN 196597-51-0 HCAPLUS

CN Propanamide, N-[2-(1,2,3,7,8,9-hexahydroindeno[5,4-b][1,4]oxazin-9-yl)ethyl]- (9CI) (CA INDEX NAME)

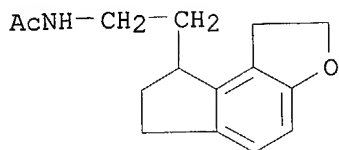


IT 196597-16-7P 196597-17-8P 196597-28-1P

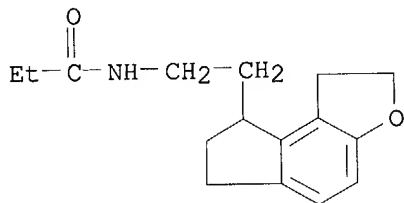
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and melatonin receptor affinity of tricyclic indanes via Horner-Emmons reaction of furanoindanone with di-Et cyanomethylphosphonate followed by hydrogenation and amidation)

RN 196597-16-7 HCAPLUS

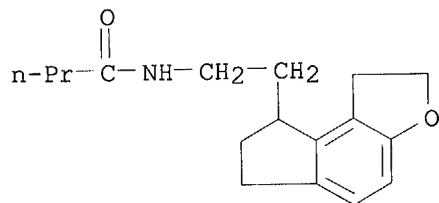
CN Acetamide, N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]- (9CI) (CA INDEX NAME)



RN 196597-17-8 HCAPLUS
 CN Propanamide, N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]-
 (9CI) (CA INDEX NAME)



RN 196597-28-1 HCAPLUS
 CN Butanamide, N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]-
 (9CI) (CA INDEX NAME)

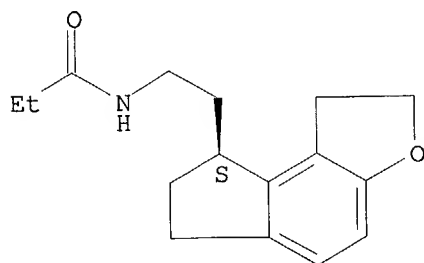


IT **196597-26-9P**

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL
 (Biological study); PREP (Preparation)
 (stereoselective preparation and melatonin receptor affinity of
 furanoindenyl derivative via bromination of chiral methoxyindenyl derivative
 followed by demethylation, allylation, Claisen rearrangement,
 ozonolysis, hydrogenation, and cyclization)

RN 196597-26-9 HCAPLUS
 CN Propanamide, N-[2-[(8S)-1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-
 yl]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



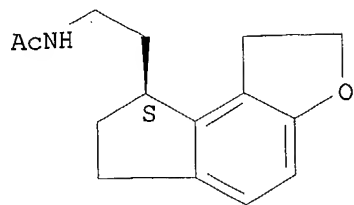
REFERENCE COUNT: 72 THERE ARE 72 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 11 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2002:391566 HCAPLUS
 DOCUMENT NUMBER: 136:391023
 TITLE: Pharmaceutical compositions containing copolyvidone
 INVENTOR(S): Ishida, Hajime; Fukuta, Makoto
 PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan
 SOURCE: PCT Int. Appl., 78 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|------------|
| WO 2002040054 | A1 | 20020523 | WO 2001-JP10016 | 20011116 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 2002014305 | A5 | 20020527 | AU 2002-14305 | 20011116 |
| JP 2002212063 | A2 | 20020731 | JP 2001-351013 | 20011116 |
| EP 1334732 | A1 | 20030813 | EP 2001-982812 | 20011116 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| US 2004018239 | A1 | 20040129 | US 2003-416172 | 20030508 |
| PRIORITY APPLN. INFO.: | | | JP 2000-351223 | A 20001117 |
| | | | WO 2001-JP10016 | W 20011116 |

OTHER SOURCE(S): MARPAT 136:391023
 AB Disclosed is a stabilized pharmaceutical composition which comprises a drug unstable in polyethylene glycol-containing preps., and a coating agent which comprises a copolyvidone and with which the drug is coated instead of polyethylene glycol. An original tablet containing (S)-N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide 4, lactose 101.6, corn starch 20, hydroxypropyl cellulose 4, and magnesium stearate 0.4 mg was coated with a coating material containing hydroxypropyl Me cellulose 3.74, copolyvidone 0.75, titanium oxide 0.5, and yellow iron oxide 0.01 mg to obtain a film-coated tablet. The obtained tablet showed improved storage stability as compare with a tablet without containing copolyvidone.
 IT **326793-94-6P**, (S)-N-[2-(1,6,7,8-Tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]acetamide
 RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (pharmaceutical compns having improved storage stability containing copolyvidone)
 RN 326793-94-6 HCAPLUS
 CN Acetamide, N-[2-[(8S)-1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

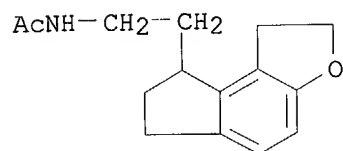


IT 196597-16-7 196597-17-8 196597-26-9
196597-28-1

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical comps having improved storage stability containing
copolyvidone)

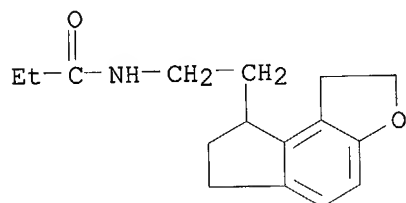
RN 196597-16-7 HCAPLUS

CN Acetamide, N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]-
(9CI) (CA INDEX NAME)



RN 196597-17-8 HCAPLUS

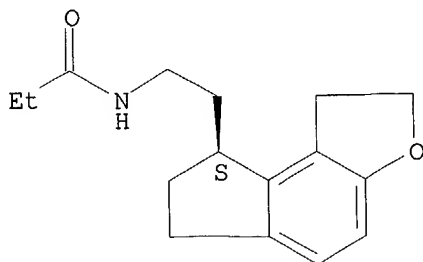
CN Propanamide, N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]-
(9CI) (CA INDEX NAME)



RN 196597-26-9 HCAPLUS

CN Propanamide, N-[2-[(8S)-1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl]ethyl]- (9CI) (CA INDEX NAME)

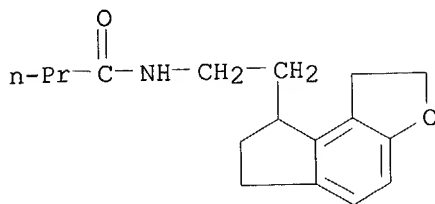
Absolute stereochemistry. Rotation (-).



RN 196597-28-1 HCAPLUS

CN Butanamide, N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]-

(9CI) (CA INDEX NAME)



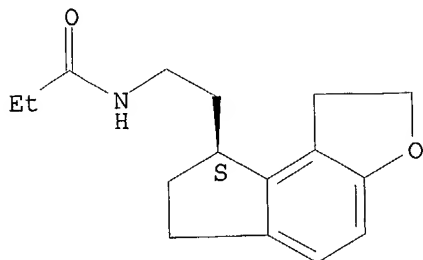
REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 12 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2002:391565 HCAPLUS
 DOCUMENT NUMBER: 136:391022
 TITLE: Pharmaceutical compositions containing talc and/or barium sulfate
 INVENTOR(S): Fukuta, Makoto; Ishida, Hajime
 PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan
 SOURCE: PCT Int. Appl., 49 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|--|----------|-----------------|------------|
| WO 2002040053 | A1 | 20020523 | WO 2001-JP10017 | 20011116 |
| W: | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | |
| RW: | GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | |
| AU 2002014306 | A5 | 20020527 | AU 2002-14306 | 20011116 |
| JP 2002212104 | A2 | 20020731 | JP 2001-351137 | 20011116 |
| PRIORITY APPLN. INFO.: | | | JP 2000-351226 | A 20001117 |
| | | | WO 2001-JP10017 | W 20011116 |

OTHER SOURCE(S): MARPAT 136:391022
 AB Disclosed is a stabilized pharmaceutical composition which comprises a drug unstable in titanium oxide-containing prepns., and a coating agent which contains talc or/and barium sulfate serving as a light-shielding agent and with which the drug is coated. An original tablet containing (S)-N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide 4, lactose 101.6, corn starch 20, hydroxypropyl cellulose 4, magnesium stearate 0.4 mg was coated with a coating material containing hydroxypropyl Me cellulose 3.74, polyethylene glycol 0.75, talc 0.5, and yellow iron oxide to obtain a film-coated tablet, and tested for its storage stability.
 IT 196597-26-9
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses) (pharmaceutical compns. containing talc and/or barium sulfate as light-shielding agents)
 RN 196597-26-9 HCAPLUS
 CN Propanamide, N-[2-[(8S)-1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 13 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:366756 HCAPLUS

DOCUMENT NUMBER: 137:304205

TITLE: Three-dimensional quantitative structure-activity relationship of arylalkylamine N-acetyltransferase (AANAT) inhibitors: a comparative molecular field analysis

AUTHOR(S): Chavatte, Philippe; Yous, Said; Beaurain, Nathalie; Mesangeau, Christophe; Ferry, Gilles; Lesieur, Daniel
CORPORATE SOURCE: Laboratoire de Chimie Therapeutique, Faculte des Sciences Pharmaceutiques et Biologiques, Lille, 59006, Fr.

SOURCE: Quantitative Structure-Activity Relationships (2002), Volume Date 2001, 20(5-6), 414-421
CODEN: QSARDI; ISSN: 0931-8771

PUBLISHER: Wiley-VCH Verlag GmbH

DOCUMENT TYPE: Journal

LANGUAGE: English

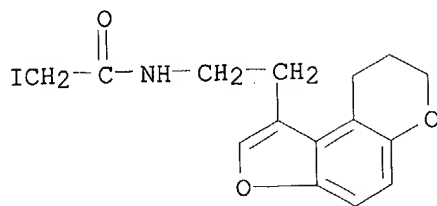
AB The three-dimensional quant. structure-activity relationship (3D-QSAR) approach using comparative mol. field anal. (CoMFA) was applied to a series of 40 compds. synthesized in our laboratory and evaluated as AANAT inhibitors. The N-bromoacetyltryptamine conformation derived from the x-ray crystal structure of the enzyme bound with a bisubstrate analog, was used to obtain the putative bioactive conformation of these inhibitors. Five statistically significant models were obtained from the randomly constituted training sets (30 compds.) and subsequently validated with the corresponding test sets (10 compds.). The best predictive model (n = 30, q² = 0.644, N = 6, r² = 0.966, s = 0.145, F = 109.478) can predict inhibitory activity for a wide range of compds. and offers important structural insight into designing novel AANAT inhibitors prior to their synthesis.

IT 251360-39-1 251360-41-5

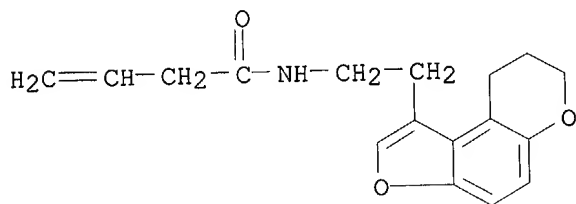
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(three-dimensional quant. structure-activity relationship of arylalkylamine N-acetyltransferase inhibitors)

RN 251360-39-1 HCAPLUS

CN Acetamide, N-[2-(8,9-dihydro-7H-furo[3,2-f][1]benzopyran-1-yl)ethyl]-2-iodo- (9CI) (CA INDEX NAME)



RN 251360-41-5 HCAPLUS
 CN 3-Butenamide, N-[2-(8,9-dihydro-7H-furo[3,2-f][1]benzopyran-1-yl)ethyl]-
 (9CI) (CA INDEX NAME)



REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 14 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:231483 HCAPLUS

DOCUMENT NUMBER: 136:400631

TITLE: Kinetic resolution of an indan derivative using
 Bacillus sp. SUI-12: synthesis of a key intermediate
 of the melatonin receptor agonist TAK-375

AUTHOR(S): Tarui, Naoki; Nagano, Yoichi; Sakane, Takeshi;
 Matsumoto, Kiyoharu; Kawada, Mitsuru; Uchikawa, Osamu;
 Ohkawa, Shigenori; Nakahama, Kazuo

CORPORATE SOURCE: Pharmaceutical Research Division, Takeda Chemical
 Industries Ltd., Osaka, 532-8686, Japan

SOURCE: Journal of Bioscience and Bioengineering (2002),
 93(1), 44-47

CODEN: JBBIF6; ISSN: 1389-1723

PUBLISHER: Society for Bioscience and Bioengineering, Japan

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The chiral indan derivative (S)-2 (2-[(8S)-1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl]ethylamine) was synthesized by enzyme-catalyzed asym. hydrolysis of the racemic acetamide 1 (N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]acetamide). The reaction was carried out using Bacillus sp. SUI-12 screened for the ability to hydrolyze 1 to give (S)-2 with high enantioselectivity. In a scaled-up experiment, a low reaction rate was observed. However, by changing the culture medium and the reaction conditions, it became possible to run the reaction to 40% conversion on a 10-g or more scale, obtaining (S)-2 at >99% enantiomeric excess (ee). The (S)-2 obtained was available for the synthesis of the melatonin receptor agonist TAK-375 (N-[2-[(8S)-1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl]ethyl]propanamide).

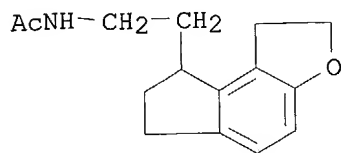
IT 196597-16-7

RL: BCP (Biochemical process); RCT (Reactant); BIOL (Biological study);

PROC (Process); RACT (Reactant or reagent)

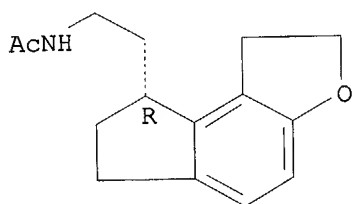
(kinetic resolution of indan derivative using Bacillus sp. SUI-12: synthesis of key intermediate of melatonin receptor agonist TAK-375)

RN 196597-16-7 HCAPLUS
 CN Acetamide, N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]-
 (9CI) (CA INDEX NAME)



IT **431063-33-1**
 RL: PEP (Physical, engineering or chemical process); PYP (Physical process); PROC (Process)
 (kinetic resolution of indan derivative using Bacillus sp. SUI-12: synthesis of key intermediate of melatonin receptor agonist TAK-375)
 RN 431063-33-1 HCAPLUS
 CN Acetamide, N-[2-[(8R)-1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl]ethyl]-
 (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 15 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2002:157751 HCAPLUS
 DOCUMENT NUMBER: 136:200089
 TITLE: Preparation of (S)-N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]acetamide as melatonin receptor antagonist and pharmaceutical compositions containing the same
 INVENTOR(S): Ohkawa, Shigenori; Miyamoto, Masaomi
 PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan
 SOURCE: PCT Int. Appl., 24 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------|--|----------|-----------------|----------|
| WO 2002016337 | A1 | 20020228 | WO 2001-JP7073 | 20010817 |
| W: | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | |
| RW: | GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, | | | |

BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
 AU 2001078754 A5 20020304 AU 2001-78754 20010817
 JP 2002128773 A2 20020509 JP 2001-247893 20010817
 PRIORITY APPLN. INFO.: JP 2000-248300 A 20000818
 WO 2001-JP7073 W 20010817

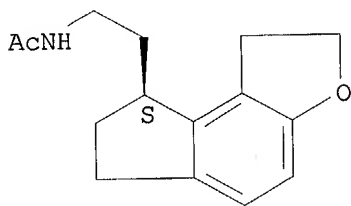
AB Provided are the title tricyclic compound (I) exhibiting an excellent affinity for melatonin receptor (ML1) and pharmaceutical compns. containing I and prodrugs thereof. I is useful as biol. rhythm regulator, sleep-awake rhythm regulator, or jet lag regulator or for the treatment of sleep disorder and circadian rhythm sleep disorder. Thus, to a solution of (S)-2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethylamine hydrochloride (71.92 g) in CH₂Cl₂ 500 mL were added 104.6 mL Et₃N, 3.67 g 4-dimethylaminopyridine, and 31.2 mL Ac₂O under ice-cooling, and the resulting mixture was stirred at room temperature for 16 h to give 72% I. A tablet and a coated tablet formulation containing I were prepared I showed IC₅₀ of 0.28 nM for inhibiting the binding of 2-[125I]iodomelatonin to a membrane sample prepared by homogenizing fore-brain of white leghorn chick.

IT **326793-94-6P**, (S)-N-[2-(1,6,7,8-Tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]acetamide
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of (S)[2-(hydro-2H-indeno[b]furanyl)ethyl]acetamide as melatonin receptor antagonist, regulator of biol. rhythm, sleep-awake, or jet lag or for treatment of sleep disorder and circadian rhythm sleep disorder)

RN 326793-94-6 HCAPLUS
 CN Acetamide, N-[2-[(8S)-1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl]ethyl]-
 (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 16 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2001:912174 HCAPLUS

DOCUMENT NUMBER: 136:635

TITLE: Use of melatoninergic ligands to obtain pharmaceutical

compositions for the prevention and treatment of development of tolerance to nitrate compounds

INVENTOR(S): O'Rourke, Stephen T.; Scalbert, Elizabeth; Delagrangé, Philippe; Bennejean, Caroline; Renard, Pierre; Vanhoutte, Paul

PATENT ASSIGNEE(S): Adir et Compagnie, Fr.

SOURCE: Fr. Demande, 17 pp.

CODEN: FRXXBL

DOCUMENT TYPE: Patent

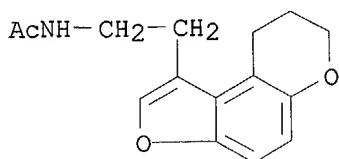
LANGUAGE: French

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------|------|-------|-----------------|-------|
| ----- | ---- | ----- | ----- | ----- |

FR 2805993 A1 20010914 FR 2000-2952 20000308
 FR 2805993 B1 20040116
 PRIORITY APPLN. INFO.: FR 2000-2952 20000308
 AB Melatoninerigic ligands are used to obtain pharmaceutical compns. for the prevention and treatment of development of tolerance to nitrate compds. Efficacy of melatonin in prevention of tolerance to 10⁻⁴ M nitroglycerin in swine coronary arteries is shown.
 IT **251360-37-9**
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (use of melatoninerigic ligands to obtain pharmaceutical compns. for prevention and treatment of development of tolerance to nitrate compds.)
 RN 251360-37-9 HCAPLUS
 CN Acetamide, N-[2-(8,9-dihydro-7H-furo[3,2-f][1]benzopyran-1-yl)ethyl]- (9CI) (CA INDEX NAME)



L29 ANSWER 17 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2001:167841 HCAPLUS
 DOCUMENT NUMBER: 134:212749
 TITLE: Matrix adhering to nasal mucosa
 INVENTOR(S): Akiyama, Yoko; Nagahara, Naoki; Bando, Hiroto
 PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan
 SOURCE: PCT Int. Appl., 34 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|------------|
| WO 2001015735 | A1 | 20010308 | WO 2000-JP5739 | 20000825 |
| W: AE, AG, AL, AM, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CN, CR, CU, CZ, DM, DZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MA, MD, MG, MK, MN, MX, MZ, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| JP 2001131057 | A2 | 20010515 | JP 2000-255493 | 20000825 |
| EP 1206943 | A1 | 20020522 | EP 2000-991043 | 20000825 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL | | | | |
| US 6663883 | B1 | 20031216 | US 2002-69072 | 20020221 |
| PRIORITY APPLN. INFO.: | | | JP 1999-240162 | A 19990826 |
| | | | WO 2000-JP5739 | W 20000825 |

OTHER SOURCE(S): MARPAT 134:212749

AB Disclosed is a matrix adhering to the nasal mucosa which allows improved transfer into the brain of a drug exerting its effect in the brain and is capable of continuously supplying the drug into the brain. This matrix contains a polyglycerol fatty acid ester, the drug exerting its effect in

the brain, and a sticky substance. Polyglycerol docosanoate (HB 310) and hydrogenated castor oil were heated. To the above mixture, cephalixin and Hiviswako 104 were added and the resulting mixture was made into granules.

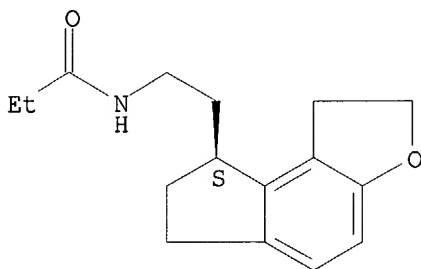
IT 196597-26-9

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(matrix adhering to nasal mucosa for improved drug transfer to brain)

RN 196597-26-9 HCAPLUS

CN Propanamide, N-[2-[(8S)-1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 18 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2001:137191 HCAPLUS

DOCUMENT NUMBER: 134:193338

TITLE: Preparation and use of condensed indoline derivatives and their use as 5-HT, in particular 5-HT_{2c}, receptor ligands

INVENTOR(S): Roffey, Jonathan Richard Anthony; Davidson, James Edward Paul; Mansell, Howard Langham; Hamlyn, Richard John; Adams, David Reginald

PATENT ASSIGNEE(S): Vernalis Research Limited, UK

SOURCE: PCT Int. Appl., 55 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-------------------|----------|
| WO 2001012602 | A1 | 20010222 | WO 2000-GB3008 | 20000804 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| BR 2000013314 | A | 20020402 | BR 2000-13314 | 20000804 |
| EP 1202964 | A1 | 20020508 | EP 2000-951696 | 20000804 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL | | | | |
| TR 200200351 | T2 | 20020621 | TR 2002-200200351 | 20000804 |
| JP 2003507366 | T2 | 20030225 | JP 2001-517500 | 20000804 |
| AU 774337 | B2 | 20040624 | AU 2000-64554 | 20000804 |

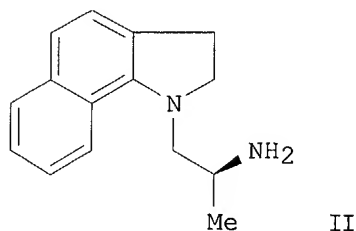
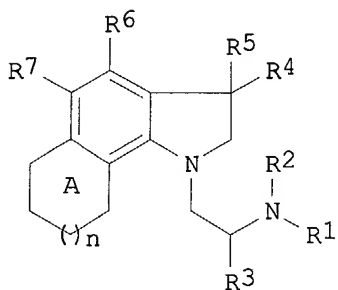
ZA 2001010218
PRIORITY APPLN. INFO.:

A 20021212
MARPAT 134:193338

ZA 2001-10218
GB 1999-18965
WO 2000-GB3008

20011212
A 19990811
W 20000804

OTHER SOURCE(S):
GI



AB Novel compds. I and use thereof are claimed [wherein; R1, R2 are H, alkyl; R3 is alkyl; R4, R5 are H, alkyl; R6, R7 are H, halo, OH, alkyl, aryl, NH2, alkylamino, dialkylamino, alkoxy, aryloxy, alkylthio, alkylsulfoxyl, alkylsulfonyl, nitro, carbonitrile, carbo-alkoxy, carbo-aryloxy and carboxyl; A is a 5- or 6-membered (un)saturated (hetero)cycle (n is 1 or 2)]. Eleven examples are given. The synthesis of II proceeded by alkylation of benz[g]indole with the corresponding N-tert-butoxycarbonyl-protected sidechain. The resulting indole was converted to the indoline with sodium cyanoborohydride in acetic acid. Deprotection with trifluoroacetic acid furnished II as an oil and isolation of a solid as its hemi-fumarate derivative. Compds. I showed affinity for 5-HT2A, 5-HT2B and 5-HT2C receptors in a CHO cell line. Compound II had a Ki of 107 nM in a radiolabeled [3H]-5-HT assay. Treatment of disorders of the central nervous system; cardiovascular disorders; gastrointestinal disorders; diabetes insipidus, and sleep apnea, and particularly the treatment of obesity are claimed uses of compds. I.

IT 327183-27-7P 327183-28-8P 327183-39-1P
327183-40-4P 327183-57-3P 327183-58-4P
327183-66-4P 327183-67-5P 327183-68-6P

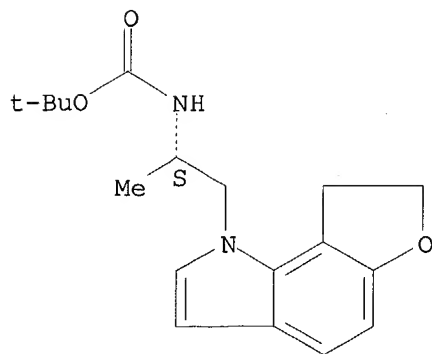
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation and use of condensed indoline derivs. and their use as 5-HT receptor ligands)

RN 327183-27-7 HCAPLUS

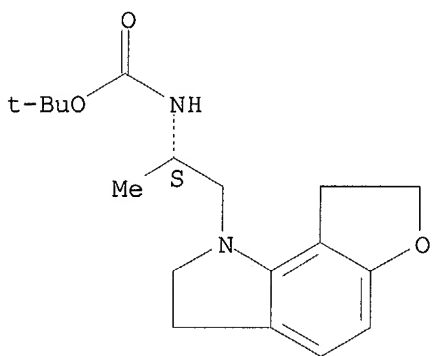
CN Carbamic acid, [(1S)-2-(7,8-dihydro-1H-furo[2,3-g]indol-1-yl)-1-methylethyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



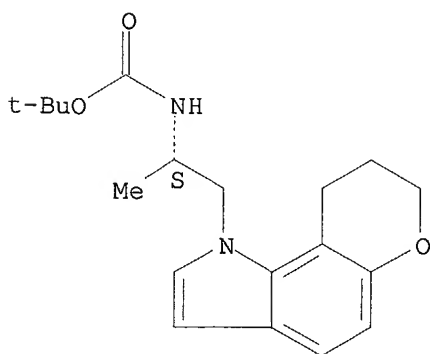
RN 327183-28-8 HCAPLUS
 CN Carbamic acid, [(1S)-1-methyl-2-(2,3,7,8-tetrahydro-1H-furo[2,3-g]indol-1-yl)ethyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



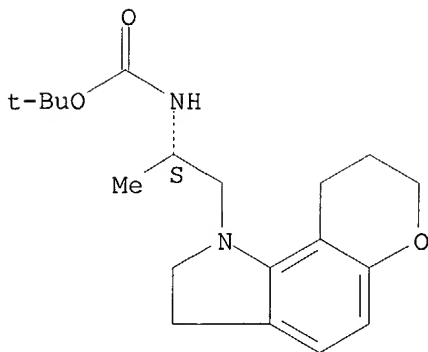
RN 327183-39-1 HCAPLUS
 CN Carbamic acid, [(1S)-2-(8,9-dihydropyrano[2,3-g]indol-1(7H)-yl)-1-methylethyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 327183-40-4 HCAPLUS
 CN Carbamic acid, [(1S)-1-methyl-2-(2,3,8,9-tetrahydropyrano[2,3-g]indol-1(7H)-yl)ethyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

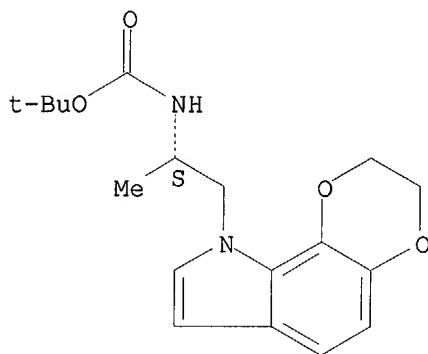
Absolute stereochemistry.



RN 327183-57-3 HCAPLUS

CN Carbamic acid, [(1S)-2-(2,3-dihydro-9H-1,4-dioxino[2,3-g]indol-9-yl)-1-methylethyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

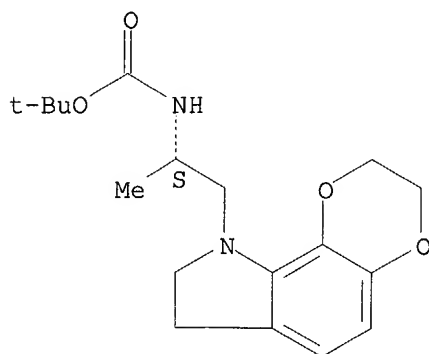
Absolute stereochemistry.



RN 327183-58-4 HCAPLUS

CN Carbamic acid, [(1S)-1-methyl-2-(2,3,7,8-tetrahydro-9H-1,4-dioxino[2,3-g]indol-9-yl)ethyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

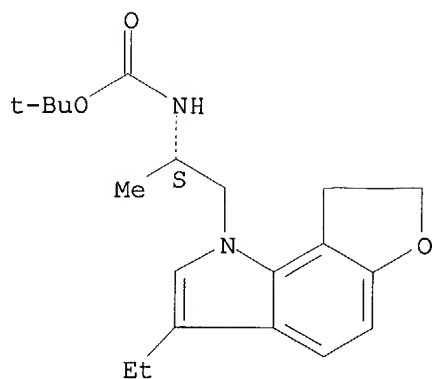
Absolute stereochemistry.



RN 327183-66-4 HCAPLUS

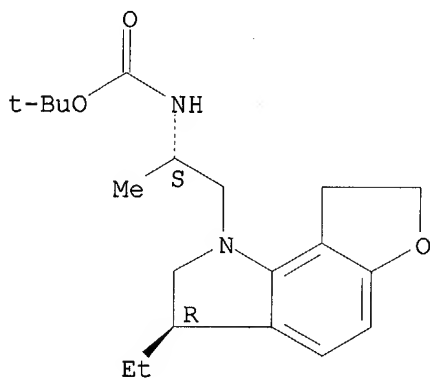
CN Carbamic acid, [(1S)-2-(3-ethyl-7,8-dihydro-1H-furo[2,3-g]indol-1-yl)-1-methylethyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



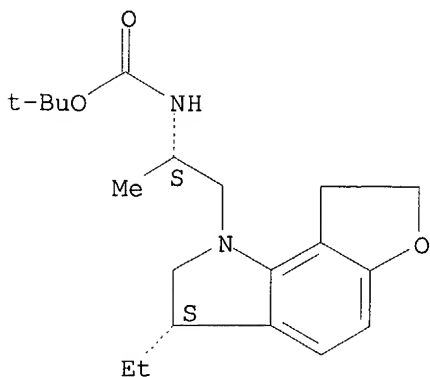
RN 327183-67-5 HCAPLUS
 CN Carbamic acid, [(1S)-2-[(3R)-3-ethyl-2,3,7,8-tetrahydro-1H-furo[2,3-g]indol-1-yl]-1-methylethyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 327183-68-6 HCAPLUS
 CN Carbamic acid, [(1S)-2-[(3S)-3-ethyl-2,3,7,8-tetrahydro-1H-furo[2,3-g]indol-1-yl]-1-methylethyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT:

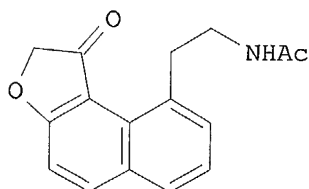
4

THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 19 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2000:381460 HCAPLUS
 DOCUMENT NUMBER: 133:17374
 TITLE: Preparation of N-aralkylacetamides and -ureas as
 melatonin receptor ligands
 INVENTOR(S): Lesieur, Daniel; Depreux, Patrick; Leclerc, Veronique;
 Mansour, Hamid Ait; Delagrange, Philippe; Renard,
 Pierre
 PATENT ASSIGNEE(S): Adir Et Compagnie, Fr.
 SOURCE: U.S., 23 pp., Cont.-in-part of U.S. Ser. No. 124,197.
 CODEN: USXXAM
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 3
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|------|----------|-----------------|-------------|
| US 6071946 | A | 20000606 | US 1999-387461 | 19990901 |
| FR 2725985 | A1 | 19960426 | FR 1994-12581 | 19941021 |
| FR 2725985 | B1 | 19961115 | | |
| US 5843986 | A | 19981201 | US 1995-545395 | 19951019 |
| US 5998461 | A | 19991207 | US 1998-124197 | 19980728 |
| PRIORITY APPLN. INFO.: | | | FR 1994-12581 | A 19941021 |
| | | | US 1995-545395 | A2 19951019 |
| | | | US 1998-124197 | A2 19980728 |

OTHER SOURCE(S): MARPAT 133:17374
 GI

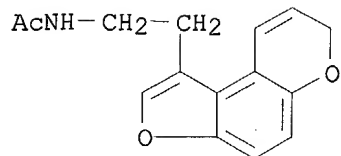


I

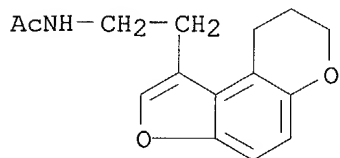
AB R1ZNR2R3 [R1 = tricyclic ring system; R2 = H or alkyl; R3 = CO(CH2)nR5,
 CONH(CH2)mR6, etc.; R5,R6 = H, alkyl, alkenyl, etc.; Z = (un)substituted
 alkylene; m,n = 0-3] were prepared as melatonin receptor ligands (no data).
 Thus, N-[2-(7-hydroxy-1-naphthyl)ethyl]acetamide was etherified by
 BrCH2CO2Et and the saponified product cyclized to give title compound I.

IT 216391-25-2P 251360-37-9P 251360-38-0P
 251360-39-1P 251360-40-4P 251360-41-5P
 251360-42-6P 272122-11-9P 272122-12-0P
 272122-17-5P 272122-18-6P 272122-19-7P
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological
 study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);
 BIOL (Biological study); PREP (Preparation); USES (Uses)
 (preparation of N-aralkylacetamides and -ureas as melatonin receptor
 ligands)

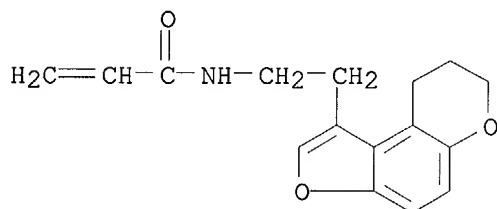
RN 216391-25-2 HCAPLUS
 CN Acetamide, N-[2-(7H-furo[3,2-f][1]benzopyran-1-yl)ethyl]- (9CI) (CA INDEX
 NAME)



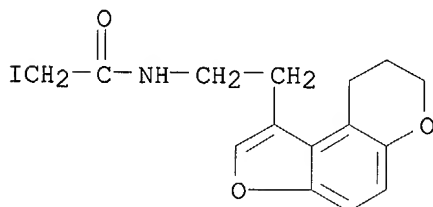
RN 251360-37-9 HCAPLUS
 CN Acetamide, N-[2-(8,9-dihydro-7H-furo[3,2-f][1]benzopyran-1-yl)ethyl]-
 (9CI) (CA INDEX NAME)



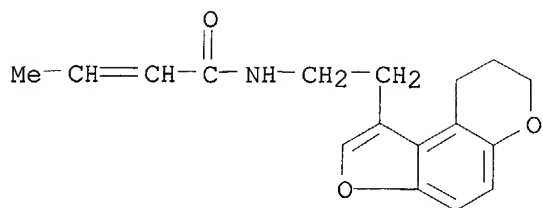
RN 251360-38-0 HCAPLUS
 CN 2-Propenamide, N-[2-(8,9-dihydro-7H-furo[3,2-f][1]benzopyran-1-yl)ethyl]-
 (9CI) (CA INDEX NAME)



RN 251360-39-1 HCAPLUS
 CN Acetamide, N-[2-(8,9-dihydro-7H-furo[3,2-f][1]benzopyran-1-yl)ethyl]-2-
 iodo- (9CI) (CA INDEX NAME)

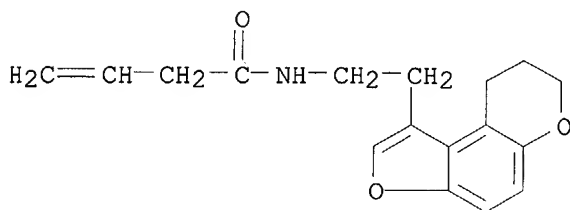


RN 251360-40-4 HCAPLUS
 CN 2-Butenamide, N-[2-(8,9-dihydro-7H-furo[3,2-f][1]benzopyran-1-yl)ethyl]-
 (9CI) (CA INDEX NAME)



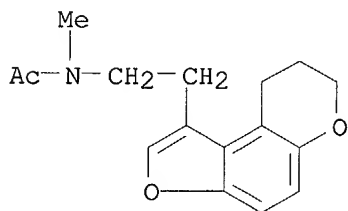
RN 251360-41-5 HCAPLUS

CN 3-Butenamide, N-[2-(8,9-dihydro-7H-furo[3,2-f][1]benzopyran-1-yl)ethyl]-
(9CI) (CA INDEX NAME)



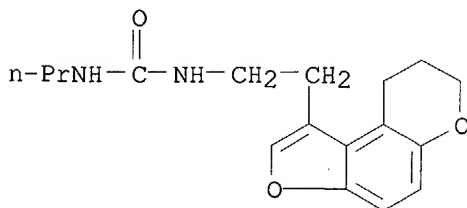
RN 251360-42-6 HCAPLUS

CN Acetamide, N-[2-(8,9-dihydro-7H-furo[3,2-f][1]benzopyran-1-yl)ethyl]-N-
methyl- (9CI) (CA INDEX NAME)



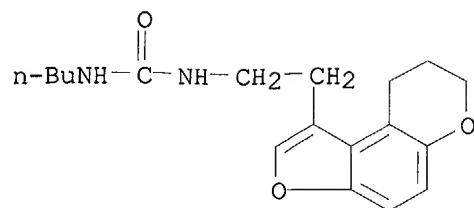
RN 272122-11-9 HCAPLUS

CN Urea, N-[2-(8,9-dihydro-7H-furo[3,2-f][1]benzopyran-1-yl)ethyl]-N'-propyl-
(9CI) (CA INDEX NAME)

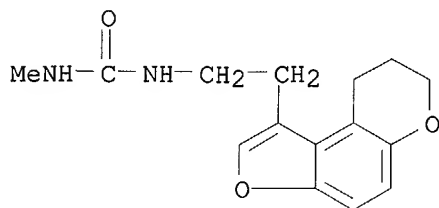


RN 272122-12-0 HCAPLUS

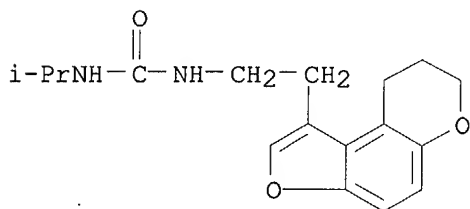
CN Urea, N-butyl-N'-[2-(8,9-dihydro-7H-furo[3,2-f][1]benzopyran-1-yl)ethyl]-
(9CI) (CA INDEX NAME)



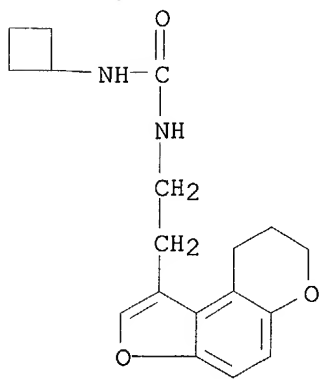
RN 272122-17-5 HCAPLUS
 CN Urea, N-[2-(8,9-dihydro-7H-furo[3,2-f][1]benzopyran-1-yl)ethyl]-N'-methyl-
 (9CI) (CA INDEX NAME)



RN 272122-18-6 HCAPLUS
 CN Urea, N-[2-(8,9-dihydro-7H-furo[3,2-f][1]benzopyran-1-yl)ethyl]-N'-(1-methylethyl)- (9CI) (CA INDEX NAME)



RN 272122-19-7 HCAPLUS
 CN Urea, N-cyclobutyl-N'-[2-(8,9-dihydro-7H-furo[3,2-f][1]benzopyran-1-yl)ethyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 20 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:183599 HCAPLUS
DOCUMENT NUMBER: 132:289039
TITLE: Pharmacological characterization of human recombinant
melatonin mt1 and MT2 receptors
AUTHOR(S): Browning, Christopher; Beresford, Isabel; Fraser,
Neil; Giles, Heather
CORPORATE SOURCE: Receptor Pharmacology Glaxo Wellcome Medicines
Research Centre, Stevenage, SG1 2NY, UK
SOURCE: British Journal of Pharmacology (2000), 129(5),
877-886
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors have pharmacol. characterized recombinant human mt1 and MT2 receptors, stably expressed in Chinese hamster ovary cells (CHO-mt1 and CHO-MT2), by measurement of [3H]-melatonin binding and forskolin-stimulated cAMP production [3H]-melatonin bound to mt1 and MT2 receptors with pK_D values of 9.89 and 9.56 and B_{max} values of 1.20 and 0.82 pmol mg⁻¹ protein, resp. While most melatonin receptor agonists had similar affinities for mt1 and MT2 receptors, a number of putative antagonists had substantially higher affinities for MT2 receptors, including luzindole (11-fold), GR128107 (23-fold) and 4-P-PDOT (61-fold). In both CHO-mt1 and CHO-MT2 cells, melatonin inhibited forskolin-stimulated accumulation of cAMP in a concentration-dependent manner (pIC₅₀ 9.53 and 9.74, resp.) causing 83 and 64% inhibition of cAMP production at 100 nM, resp. The potencies of a range of melatonin receptor agonists were determined. At MT2 receptors, melatonin, 2-iodomelatonin and 6-chloromelatonin were essentially equipotent, while at the mt1 receptor these agonists gave the rank order of potency of 2-iodomelatonin > melatonin > 6-chloromelatonin. In both CHO-mt1 and CHO-MT2 cells, melatonin-induced inhibition of forskolin-stimulated cAMP production was antagonized in a concentration-dependent manner by the melatonin receptor antagonist luzindole, with pA₂ values of 5.75 and 7.64, resp. Melatonin-mediated responses were abolished by pre-treatment of cells with pertussis toxin, consistent with activation of Gi/Go G-proteins. This is the first report of the use of [3H]-melatonin for the characterization of recombinant mt1 and MT2 receptors. The authors' results demonstrate that these receptor subtypes have distinct pharmacol. profiles.

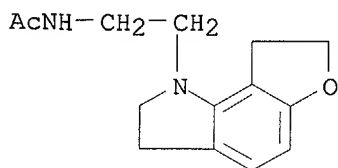
IT 170729-12-1, GR196429

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(pharmacol. characterization of human recombinant melatonin mt1 and MT2 receptors)

RN 170729-12-1 HCAPLUS

CN Acetamide, N-[2-(2,3,7,8-tetrahydro-1H-furo[2,3-g]indol-1-yl)ethyl]- (9CI)
(CA INDEX NAME)

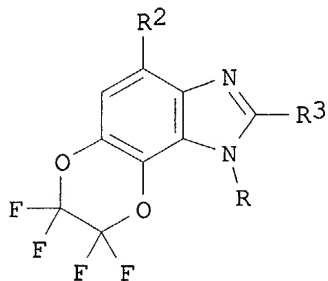


REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 21 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2000:54188 HCAPLUS
 DOCUMENT NUMBER: 132:93322
 TITLE: Preparation of dioxinobenzimidazolylmethylcarbamatesas
 protozoacides
 INVENTOR(S): Greif, Gisela; Haberkorn, Axel; Baasner, Bernd; Lieb,
 Folker; Marhold, Albrecht
 PATENT ASSIGNEE(S): Bayer A.-G., Germany
 SOURCE: Ger. Offen., 18 pp.
 CODEN: GWXXBX
 DOCUMENT TYPE: Patent
 LANGUAGE: German
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|--|------|----------|------------------|----------|
| DE 19831985 | A1 | 20000120 | DE 1998-19831985 | 19980716 |
| CA 2337351 | AA | 20000127 | CA 1999-2337351 | 19990705 |
| WO 2000004022 | A1 | 20000127 | WO 1999-EP4650 | 19990705 |
| W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 9949067 | A1 | 20000207 | AU 1999-49067 | 19990705 |
| BR 9912126 | A | 20010410 | BR 1999-12126 | 19990705 |
| EP 1097154 | A1 | 20010509 | EP 1999-932812 | 19990705 |
| EP 1097154 | B1 | 20031001 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| JP 2002520414 | T2 | 20020709 | JP 2000-560128 | 19990705 |
| NZ 509352 | A | 20030530 | NZ 1999-509352 | 19990705 |
| CN 1117753 | B | 20030813 | CN 1999-810383 | 19990705 |
| AT 251164 | E | 20031015 | AT 1999-932812 | 19990705 |
| ES 2211119 | T3 | 20040701 | ES 1999-932812 | 19990705 |
| US 6620833 | B1 | 20030916 | US 2001-743440 | 20010109 |
| HK 1040710 | A1 | 20040507 | HK 2002-102363 | 20020327 |
| US 2004010025 | A1 | 20040115 | US 2003-613818 | 20030703 |
| PRIORITY APPLN. INFO.: DE 1998-19831985 A 19980716 WO 1999-EP4650 W 19990705 US 2001-743440 A3 20010109 | | | | |
| OTHER SOURCE(S): MARPAT 132:93322 GI | | | | |



I

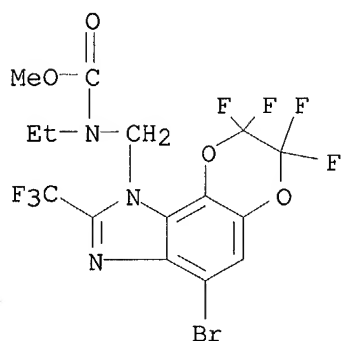
AB Title compds. (I; R = CHR1NR4CO2R5; R1 = H or alkyl; R2 = Cl or Br; R3 = fluoroalkyl; R4 = alkyl or substituted Ph; R5 = alkyl) were prepared Thus, 2,2,3,3-tetrafluoro-1,4-benzodioxin was converted in 6 steps to I (R2 = Br, R3 = CF3) (II; R = H) which was N-alkylated by ClCH2NEtCO2Me to give II (R = CH2NEtCO2Me). Data for biol. activity of I were given.

IT 254895-77-7P 254895-78-8P 254895-79-9P
254895-80-2P 254895-81-3P 254895-82-4P
254895-83-5P 254895-84-6P 254895-85-7P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of dioxinobenzimidazolylmethylcarbamates as protozoacides)

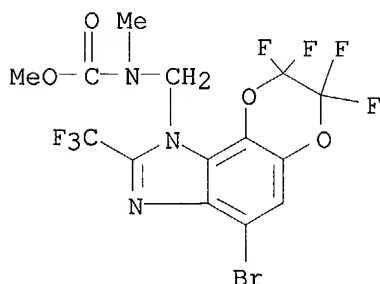
RN 254895-77-7 HCAPLUS

CN Carbamic acid, [[4-bromo-7,7,8,8-tetrafluoro-7,8-dihydro-2-(trifluoromethyl)-1H-[1,4]dioxino[2,3-e]benzimidazol-1-yl]methyl]ethyl-, methyl ester (9CI) (CA INDEX NAME)



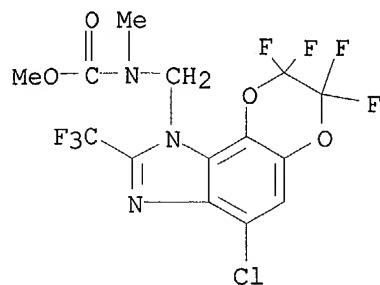
RN 254895-78-8 HCAPLUS

CN Carbamic acid, [[4-bromo-7,7,8,8-tetrafluoro-7,8-dihydro-2-(trifluoromethyl)-1H-[1,4]dioxino[2,3-e]benzimidazol-1-yl]methyl]methyl-, methyl ester (9CI) (CA INDEX NAME)

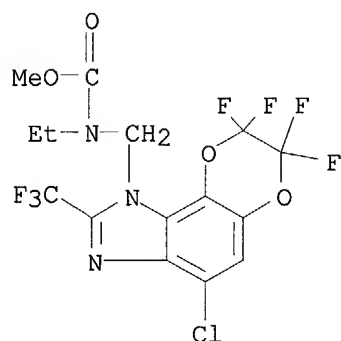


RN 254895-79-9 HCAPLUS

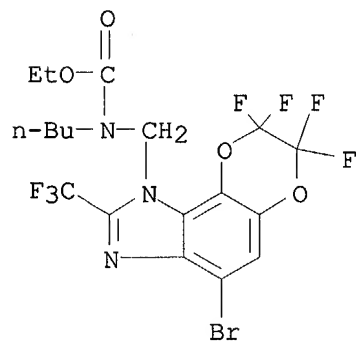
CN Carbamic acid, [[4-chloro-7,7,8,8-tetrafluoro-7,8-dihydro-2-(trifluoromethyl)-1H-[1,4]dioxino[2,3-e]benzimidazol-1-yl]methyl]methyl-, methyl ester (9CI) (CA INDEX NAME)



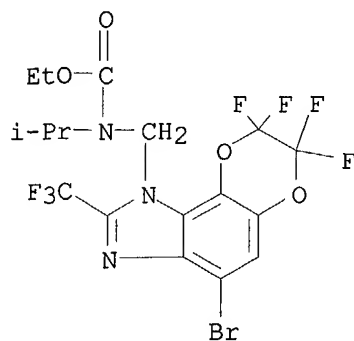
RN 254895-80-2 HCAPLUS
 CN Carbamic acid, [[4-chloro-7,7,8,8-tetrafluoro-7,8-dihydro-2-(trifluoromethyl)-1H-[1,4]dioxino[2,3-e]benzimidazol-1-yl]methyl]ethyl-, methyl ester (9CI) (CA INDEX NAME)



RN 254895-81-3 HCAPLUS
 CN Carbamic acid, [[4-bromo-7,7,8,8-tetrafluoro-7,8-dihydro-2-(trifluoromethyl)-1H-[1,4]dioxino[2,3-e]benzimidazol-1-yl]methyl]butyl-, ethyl ester (9CI) (CA INDEX NAME)

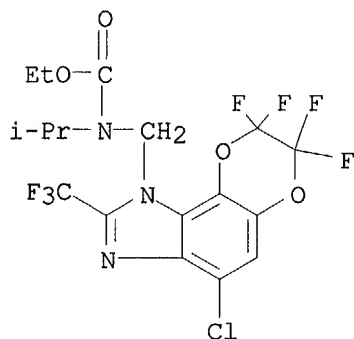


RN 254895-82-4 HCAPLUS
 CN Carbamic acid, [[4-bromo-7,7,8,8-tetrafluoro-7,8-dihydro-2-(trifluoromethyl)-1H-[1,4]dioxino[2,3-e]benzimidazol-1-yl]methyl] (1-methylethyl)-, ethyl ester (9CI) (CA INDEX NAME)



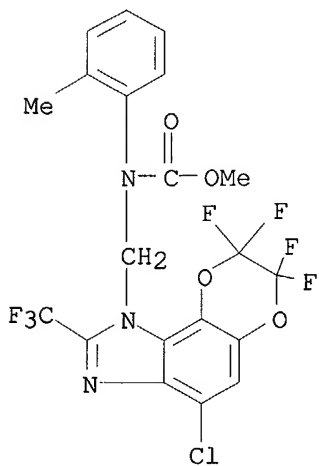
RN 254895-83-5 HCAPLUS

CN Carbamic acid, [[4-chloro-7,7,8,8-tetrafluoro-7,8-dihydro-2-(trifluoromethyl)-1H-[1,4]dioxino[2,3-e]benzimidazol-1-yl]methyl] (1-methylethyl)-, ethyl ester (9CI) (CA INDEX NAME)



RN 254895-84-6 HCAPLUS

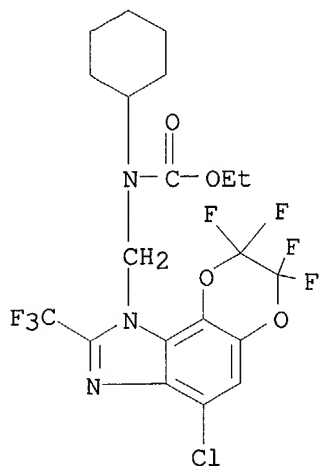
CN Carbamic acid, [[4-chloro-7,7,8,8-tetrafluoro-7,8-dihydro-2-(trifluoromethyl)-1H-[1,4]dioxino[2,3-e]benzimidazol-1-yl]methyl] (2-methylphenyl)-, methyl ester (9CI) (CA INDEX NAME)



RN 254895-85-7 HCAPLUS

CN Carbamic acid, [[4-chloro-7,7,8,8-tetrafluoro-7,8-dihydro-2-(trifluoromethyl)-1H-[1,4]dioxino[2,3-e]benzimidazol-1-

yl)methyl]cyclohexyl-, ethyl ester (9CI) (CA INDEX NAME)



L29 ANSWER 22 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 1999:795635 HCAPLUS
 DOCUMENT NUMBER: 132:40535
 TITLE: Pharmaceutical composition for treating or preventing sleep disorders
 INVENTOR(S): Ohkawa, Shigenori; Miyamoto, Masaomi
 PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan
 SOURCE: PCT Int. Appl., 25 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|------------|
| WO 9963977 | A2 | 19991216 | WO 1999-JP3057 | 19990608 |
| WO 9963977 | A3 | 20010329 | | |
| W: AE, AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| CA 2332521 | AA | 19991216 | CA 1999-2332521 | 19990608 |
| AU 9940605 | A1 | 19991230 | AU 1999-40605 | 19990608 |
| JP 2000063272 | A2 | 20000229 | JP 1999-160568 | 19990608 |
| JP 3509637 | B2 | 20040322 | | |
| EP 1100508 | A2 | 20010523 | EP 1999-923960 | 19990608 |
| EP 1100508 | B1 | 20030827 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI | | | | |
| AT 247967 | E | 20030915 | AT 1999-923960 | 19990608 |
| US 6348485 | B1 | 20020219 | US 2000-700405 | 20001114 |
| PRIORITY APPLN. INFO.: | | | | |
| | | | JP 1998-160270 | A 19980609 |
| | | | WO 1999-JP3057 | W 19990608 |

AB The present invention provides a pharmaceutical composition for treating or preventing sleep disorders which comprises (S)-N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide (I) in combination with at

least 1 active component selected from zolpidem, zopiclone, triazolam and brotizolam. Thus, I was obtained in a series of steps starting from 2,3-dihydrobenzofuran-5-carbaldehyde. Tablets were prepared from I 10.0, lactose 60.0, corn starch 35.0, gelatin 3.0, and Mg stearate 2.0 g. Treatment with compound I (0.003 mg/kg, p.o.) had no significant effects on the latency of any sleep stages. Treatment with triazolam alone (0.03 mg/kg) did not affect general behavior and it did not cause ataxia and sedation as such were seen when high doses of triazolam are given. Co-administration of I and triazolam shortened the latencies of deep slow wave sleep, stage 3 and stage 4, and it significantly shortened the latency of the stage 4 sleep. The co-administration also had no significant effects on general behavior of monkeys.

IT 196597-26-9P

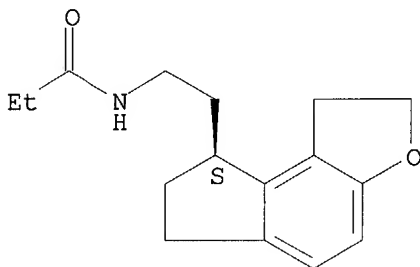
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(pharmaceutical composition for treating or preventing sleep disorders)

RN 196597-26-9 HCAPLUS

CN Propanamide, N-[2-[(8S)-1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L29 ANSWER 23 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1999:779227 HCAPLUS

DOCUMENT NUMBER: 132:12253

TITLE: Preparation of N-(naphthofuranylethyl)acetamides and analogs as melatonin receptor ligands

INVENTOR(S): Lesieur, Daniel; Depreux, Patrick; Leclerc, Ve'ronique; Mansour, Hamid Ait; Delagrangre, Philippe; Renard, Pierre

PATENT ASSIGNEE(S): Adir et Compagnie, Fr.

SOURCE: U.S., 25 pp., Cont.-in-part of U.S. 5,843,986.

CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

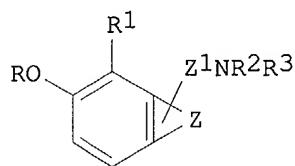
FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

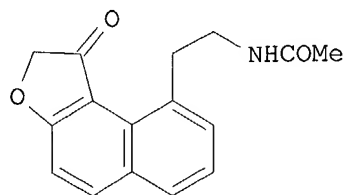
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|------|----------|-----------------|-------------|
| US 5998461 | A | 19991207 | US 1998-124197 | 19980728 |
| FR 2725985 | A1 | 19960426 | FR 1994-12581 | 19941021 |
| FR 2725985 | B1 | 19961115 | | |
| US 5843986 | A | 19981201 | US 1995-545395 | 19951019 |
| US 6071946 | A | 20000606 | US 1999-387461 | 19990901 |
| PRIORITY APPLN. INFO.: | | | FR 1994-12581 | A 19941021 |
| | | | US 1995-545395 | A2 19951019 |
| | | | US 1998-124197 | A2 19980728 |

OTHER SOURCE(S): MARPAT 132:12253

GI



I



II

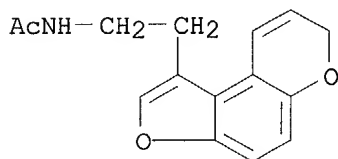
AB Title compds. [I; RR1 = (un)substituted (oxo)alk(en)ylene, -(oxo)alkynylene; R2 = H or alkyl; R3 = CO(CH2)nR5, CONH(CH2)mR6, etc.; R5, R6 = H, (cyclo)alkyl, alkenyl, etc.; Z = CH:CHCH:CH, CH:CHX, etc.; X = O, S, NH; Z1(un)substituted alkylene; m, n = 0-3] were prepared. Thus, N-[2-(7-hydroxy-1-naphthyl)ethyl]acetamide was etherified by BrCH2CO2Et and the saponified product cyclized to give title compound II. Data for biol. activity of I were given.

IT 216391-25-2P 251360-35-7P 251360-37-9P
251360-38-0P 251360-39-1P 251360-40-4P
251360-41-5P 251360-42-6P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of N-(naphthofuranylethyl)acetamides and analogs as melatonin receptor ligands)

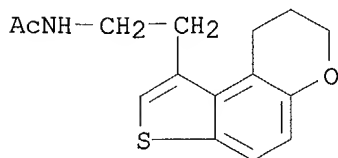
RN 216391-25-2 HCAPLUS

CN Acetamide, N-[2-(7H-furo[3,2-f][1]benzopyran-1-yl)ethyl]- (9CI) (CA INDEX NAME)



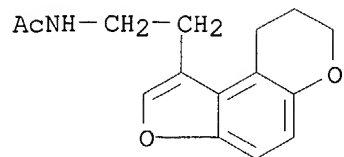
RN 251360-35-7 HCAPLUS

CN Acetamide, N-[2-(8,9-dihydro-7H-thieno[3,2-f][1]benzopyran-1-yl)ethyl]- (9CI) (CA INDEX NAME)

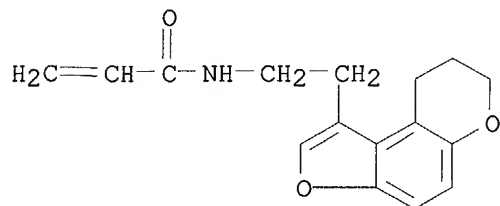


RN 251360-37-9 HCAPLUS

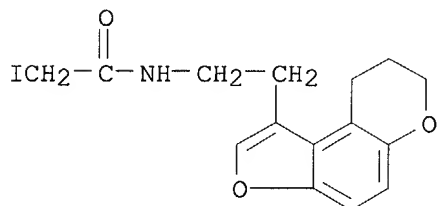
CN Acetamide, N-[2-(8,9-dihydro-7H-furo[3,2-f][1]benzopyran-1-yl)ethyl]- (9CI) (CA INDEX NAME)



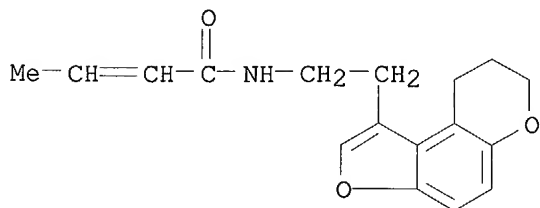
RN 251360-38-0 HCAPLUS
 CN 2-Propenamide, N-[2-(8,9-dihydro-7H-furo[3,2-f][1]benzopyran-1-yl)ethyl]-
 (9CI) (CA INDEX NAME)



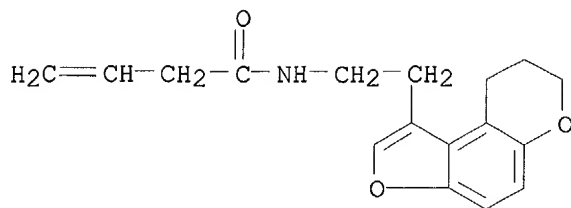
RN 251360-39-1 HCAPLUS
 CN Acetamide, N-[2-(8,9-dihydro-7H-furo[3,2-f][1]benzopyran-1-yl)ethyl]-2-
 iodo- (9CI) (CA INDEX NAME)



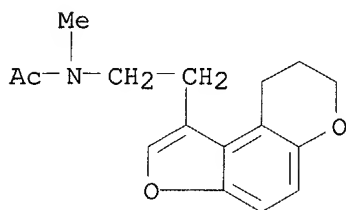
RN 251360-40-4 HCAPLUS
 CN 2-Butenamide, N-[2-(8,9-dihydro-7H-furo[3,2-f][1]benzopyran-1-yl)ethyl]-
 (9CI) (CA INDEX NAME)



RN 251360-41-5 HCAPLUS
 CN 3-Butenamide, N-[2-(8,9-dihydro-7H-furo[3,2-f][1]benzopyran-1-yl)ethyl]-
 (9CI) (CA INDEX NAME)



RN 251360-42-6 HCAPLUS
 CN Acetamide, N-[2-(8,9-dihydro-7H-furo[3,2-f][1]benzopyran-1-yl)ethyl]-N-methyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 24 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1999:765097 HCAPLUS

DOCUMENT NUMBER: 132:31090

TITLE: Novel non-indolic melatonin receptor agonists differentially entrain endogenous melatonin rhythm and increase its amplitude

AUTHOR(S): Drijfhout, Willem J.; De Vries, Jan B.; Homan, Evert J.; Brons, Heleen F.; Coppinga, Swier; Gruppen, Gert; Beresford, Isabel J. M.; Hagan, Russell M.; Grol, Cor J.; Westerink, Ben H. C.

CORPORATE SOURCE: University Centre for Pharmacy, Department of Medicinal Chemistry, University of Groningen, Groningen, 9713, Neth.

SOURCE: European Journal of Pharmacology (1999), 382(3), 157-166

CODEN: EJPHAZ; ISSN: 0014-2999

PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB In this study the authors have examined the ability of melatonin and four synthetic melatonin receptor agonists to entrain endogenous melatonin secretion in rats, free running in constant darkness. The circadian melatonin profile was measured by transpineal microdialysis, which not only reveals the time of onset and end of production (phase), but also the amplitude of the rhythm. Exogenous melatonin given at the onset of subjective darkness (clock time 12 h) was effective to entrain endogenous melatonin production. Only one agonist, 2-chloroacetamido-8-methoxytetralin (AH-017), mimicked this action. Two other agonists, 4-methoxy-2-(methylene propylamide)indan (GG-012) and N-[2-[2,3,7,8-tetrahydro-1H-furo(2,3-g)indol-1-yl]ethyl]acetamide (GR196429), induced a phase-delay under free running conditions, possibly by increasing tau (τ) period. One agonist, 2-acetamido-8-methoxytetralin (AH-001) did not show any phase effect on the free running rhythm. Unexpectedly, all melatonin receptor agonists increased the amplitude of melatonin secretion. The amount of the

increase varied from just below the level of significance (AH-001) to an approx. 2-fold increase (GG-012 and GR196429). This is in clear contrast to entrainment with melatonin, which significantly decreased the amplitude. It is hypothesized that entrainment and effects on amplitude of melatonin secretion are mediated by different mechanisms which can be differentially modulated using specific ligands.

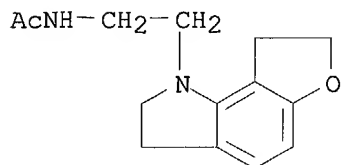
IT 170729-12-1, GR196429

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(non-indolic melatonin receptor agonists differentially entrain endogenous melatonin rhythm and increase amplitude)

RN 170729-12-1 HCAPLUS

CN Acetamide, N-[2-(2,3,7,8-tetrahydro-1H-furo[2,3-g]indol-1-yl)ethyl]- (9CI)
(CA INDEX NAME)



REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 25 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1999:332978 HCAPLUS

DOCUMENT NUMBER: 131:44725

TITLE: Preparation of optical active 2-(1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-yl)ethylamine derivative by asymmetric hydrogenation of 2-(1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-ylidene)ethylamine derivative

INVENTOR(S): Imai, Takashi; Miura, Takashi; Unrin, Hidenori; Hara, Yukio

PATENT ASSIGNEE(S): Takasago Perfumery Co., Ltd., Japan; Takeda Chemical Industries, Ltd.

SOURCE: Jpn. Kokai Tokkyo Koho, 16 pp.

CODEN: JKXXAF

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|------|----------|-----------------|----------|
| JP 11140073 | A2 | 19990525 | JP 1998-29842 | 19980212 |
| PRIORITY APPLN. INFO.: | | | JP 1997-29320 | 19970213 |
| | | | JP 1997-242546 | 19970908 |

OTHER SOURCE(S): CASREACT 131:44725; MARPAT 131:44725

GI For diagram(s), see printed CA Issue.

AB The optically active title amines [I; R₁, R₂ = H, (un)substituted hydrocarbyl or heterocyclyl; or CR₁R₂ forms a (un)substituted spiro ring; X = (CH₂)_n, NH, O, S; n = 1-4; m = 1-3; ring A may possess substituents] or salts thereof, which are useful as drugs having affinity to melatonin receptor or intermediates thereof, are prepared by asym. hydrogenation of 2-(1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-ylidene)ethylamine derivs. (II or III; R₁, R₂, X, m = same as above) in the presence of transition metal-optically active phosphine complex. Transition metal-optically active phosphine complexes are selected from Ru₂Cl₄[(R)-BINAP]₂Net₃, {RuCl(benzene)}[(R)-BINAP]Cl, {RuCl(p-cymene)}[(R)-BINAP]Cl, {RuBr(p-cymene)}[(R)-BINAP]Br, {RuI(p-cymene)}[(R)-BINAP]I₃, and

{RuI(p-cymene)[(R)-BINAP]}I. Thus, di-Et cyanomethylphosphonate was stirred with NaH in THF under ice-cooling for 30 min and then condensed with 1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one at room temperature for 1 h to give 75% (E)-2-(1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-ylidene)acetonitrile which was hydrogenated over Raney cobalt in ethanol and 3 M NH₃/ethanol at H pressure of 5.0-5.5 atm at 40° for 6 h to give, after acidification with ethanolic HCl, 89% (E)-2-(1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-ylidene)ethylamine hydrochloride. The latter compound was hydrogenated in the presence of Ru₂Cl₄[(R)-BINAP]2NEt₃ in MeOH at H pressure of 100 atm and 50° for 20 h to give (S)-2-(1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-yl)ethylamine (IV) of 88.88 %ee which was acidified with HCl to convert it into HCl salt and crystallized from MeOH and acetone and then recrystd. from MeOH and acetone to give 68% IV.HCl of 100 %ee.

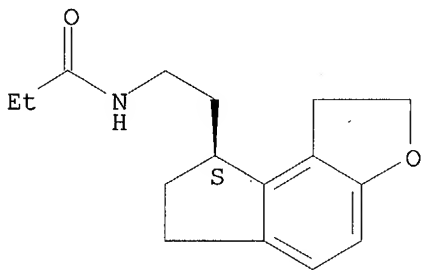
IT 196597-26-9P

RL: SPN (Synthetic preparation); PREP (Preparation)
 (preparation of optical active (tetrahydro-8H-indeno[5,4-b]furanyl)ethylamine derivative by asym. hydrogenation of (tetrahydro-8H-indeno[5,4-b]furanylidene)ethylamine derivative)

RN 196597-26-9 HCAPLUS

CN Propanamide, N-[2-[(8S)-1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L29 ANSWER 26 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1999:206865 HCAPLUS

DOCUMENT NUMBER: 130:252236

TITLE: Preparation of optically active indenofurans as intermediates for pharmaceuticals for treatment of sleep disorder

INVENTOR(S): Yamano, Toru; Adachi, Mari; Kawada, Mitsuru

PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan

SOURCE: Jpn. Kokai Tokkyo Koho, 15 pp.

CODEN: JKXXAF

DOCUMENT TYPE: Patent

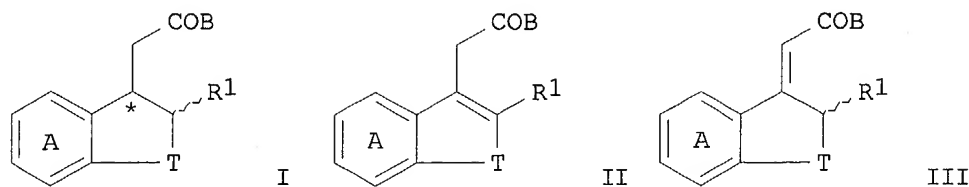
LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|------|--|-----------------|----------|
| JP 11080106 | A2 | 19990326 | JP 1997-241520 | 19970905 |
| PRIORITY APPLN. INFO.: | | | JP 1997-241520 | 19970905 |
| OTHER SOURCE(S): | | CASREACT 130:252236; MARPAT 130:252236 | | |

GI



AB Title compds. I (R1 = H, (substituted) hydrocarbon, (substituted) heterocycle; B = H, group connected with O, N, or S; T = (CH₂)_m; m = 1-4; ring A may have substituents and form fused ring with one 5- or 6-membered heterocycle) or their salts, useful as intermediates for compds. having affinity for melatonin receptor, are prepared by asym. hydrogenation of indenofurans II (R1, A, B, T = same as I), III (R1, A, B, T = same as I), or their salts in the presence of transition metal-optically active phosphine complexes. 2-(1,6-Dihydro-2H-indeno[5,4-b]furan-8-yl)acetamide was hydrogenated with Ru(OCOME)₂[(R)-BINAP] in EtOH under 100 atm H at 50° for 6 h to give 92% (S)-2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)acetamide with 92% e.e., from which (S)-N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide was prepared via two steps.

IT **196597-26-9P**

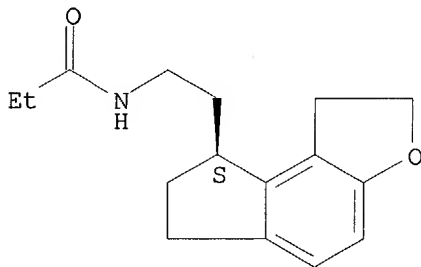
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of optically active hydroindenofurans by asym. hydrogenation of indenofurans with metal-phosphine catalysts)

RN 196597-26-9 HCAPLUS

CN Propanamide, N-[2-[(8S)-1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L29 ANSWER 27 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1998:789140 HCAPLUS

DOCUMENT NUMBER: 130:25076

TITLE: Chromenes and benzodioxins as melatonin receptor agonists

INVENTOR(S): Guillaumet, Gerald; Viaud, Marie-claude; Mamai, Ahmed; Charton, Isabelle; Renard, Pierre; Bennejean, Caroline; Guardiola, Beatrice; Daubos, Philippe

PATENT ASSIGNEE(S): Adir et Compagnie, Fr.

SOURCE: PCT Int. Appl., 142 pp.

CODEN: PIXXD2

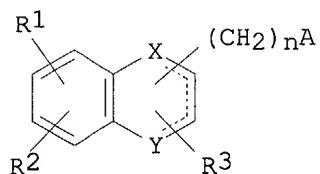
DOCUMENT TYPE: Patent

LANGUAGE: French

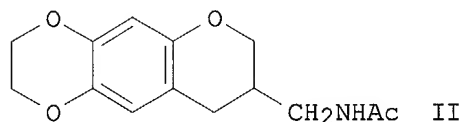
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|--|------|------------------|-----------------|-------------|
| WO 9852935 | A1 | 19981126 | WO 1998-FR954 | 19980514 |
| W: AU, BR, CA, CN, HU, JP, NO, NZ, PL, US | | | | |
| RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |
| FR 2763335 | A1 | 19981120 | FR 1997-6019 | 19970516 |
| FR 2763335 | B1 | 20001124 | | |
| AU 9877723 | A1 | 19981211 | AU 1998-77723 | 19980514 |
| AU 741753 | B2 | 20011206 | | |
| EP 998471 | A1 | 20000510 | EP 1998-925703 | 19980514 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI | | | | |
| BR 9809643 | A | 20001003 | BR 1998-9643 | 19980514 |
| JP 2002510290 | T2 | 20020402 | JP 1998-550028 | 19980514 |
| ZA 9804114 | A | 19981124 | ZA 1998-4114 | 19980515 |
| US 6313160 | B1 | 20011106 | US 1999-423745 | 19991112 |
| NO 9905594 | A | 20000114 | NO 1999-5594 | 19991115 |
| US 2002052400 | A1 | 20020502 | US 2001-941016 | 20010828 |
| US 6602903 | B2 | 20030805 | | |
| PRIORITY APPLN. INFO.: | | | FR 1997-6019 | A 19970516 |
| | | | WO 1998-FR954 | W 19980514 |
| | | | US 1999-423745 | A3 19991112 |
| OTHER SOURCE(S): | | MARPAT 130:25076 | | |
| GI | | | | |

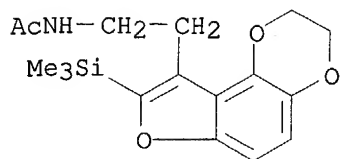


I



II

- AB Title compds. I [X, Y = S, O, SO, SO₂, CH, CH₂; R₁ = H, (un)substituted aliphatic, cycloaliph., OH, aryl, R₂ = H; R₁R₂, situated on adjacent C, form a 6-membered, optionally oxygenated, ring; R₃ = H, aryl, aralkyl, alkyl; n = 0-5; A = (un)substituted NH₂, CONH₂, CSNH₂] were prepared for use as melatonin receptor agonists (no data). Thus, the amide II was prepared from 6-acetoxy-2,3-dihydro-1,4-benzodioxin via 7-hydroxy-2,3-dihydro-1,4-benzodioxin-6-carboxaldehyde, cyclization with acrylonitrile, reduction to the amine, and acetylation.
- IT **216493-02-6P**
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
 (preparation of chromenyl- and benzodioxinylamines as melatonin receptor agonists)
- RN 216493-02-6 HCAPLUS
- CN Acetamide, N-[2-[2,3-dihydro-8-(trimethylsilyl)furo[3,2-f]-1,4-benzodioxin-9-yl]ethyl]- (9CI) (CA INDEX NAME)

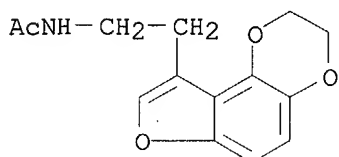


IT 216493-03-7P 216493-04-8P

RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of chromenyl- and benzodioxinylamines as melatonin receptor agonists)

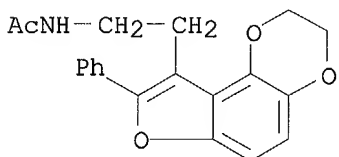
RN 216493-03-7 HCAPLUS

CN Acetamide, N-[2-(2,3-dihydrofuro[3,2-f]-1,4-benzodioxin-9-yl)ethyl]- (9CI)
(CA INDEX NAME)



RN 216493-04-8 HCAPLUS

CN Acetamide, N-[2-(2,3-dihydro-8-phenylfuro[3,2-f]-1,4-benzodioxin-9-yl)ethyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 28 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1998:727253 HCAPLUS

DOCUMENT NUMBER: 130:47746

TITLE: Pharmacological characterization of melatonin mtl receptor-mediated stimulation of [35S]-GTP γ S binding

AUTHOR(S): Beresford, Isabel J. M.; Harvey, Fiona J.; Hall, David A.; Giles, Heather

CORPORATE SOURCE: Receptor Pharmacology, Glaxo Wellcome Medicines Research Centre, Stevenage, SG1 2NY, UK

SOURCE: Biochemical Pharmacology (1998), 56(9), 1167-1174
CODEN: BCPA6; ISSN: 0006-2952

PUBLISHER: Elsevier Science Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The activation of G-proteins by melatonin mtl receptors was studied by measuring [35S]-guanosine-5'-(3-thiotriphosphate) ([35S]-GTP γ S) binding to membranes prepared from Chinese hamster ovary (CHO) cells stably expressing human mtl receptors. Melatonin stimulated [35S]-GTP γ S binding in a concentration-dependent manner (pEC₅₀, 8.77 \pm 0.02). The optimal

(212±4%) increase over basal levels of binding (basal = 100%) was observed following incubation of membranes (12.5 µg protein/well) for 120 min at 30° with [35S]-GTPγS (0.1 nM), in the presence of GDP (10 µM), NaCl (100 mM), and MgCl₂ (10 mM). Melatonin analogs stimulated [35S]-GTPγS binding with a rank order (2-iodomelatonin > melatonin = S20098 > GR196429 > 6-chloromelatonin = 6-hydroxymelatonin » N-acetylserotonin ≥ GR135531 = mt1 luzindole = 5-HT = 0), which was identical to their affinities for the high affinity state of the receptor (correlation coefficient 0.94). All agonists evoked similar maximum increases in [35S]-GTPγS binding. EC₅₀ values were 14- to 63-fold lower than binding affinities. The melatonin receptor antagonist luzindole (0.1-10 µM) evoked a parallel rightward shift in the melatonin concentration-response curve, with a pK_B of 7.19±0.13, which is similar to its affinity in radioligand binding studies for human mt1 receptors. Stimulation of [35S]-GTPγS binding was abolished by pretreatment of cells with pertussis toxin (18 h, 100 ng/mL) prior to preparation of membranes. Melatonin was without effect in CHO cells which lacked the mt1 receptor. Thus, melatonin and melatonin analogs stimulate [35S]-GTPγS binding with a profile which is consistent with binding to mt1 receptors causing activation of Gi/Go G-proteins.

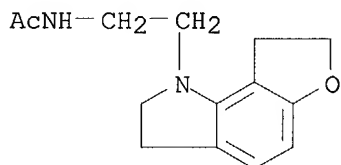
IT 170729-12-1, GR196429

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(melatonin and melatonin analogs stimulate [35S]-GTPγS binding with a profile which is consistent with binding to mt1 receptors causing activation of Gi/Go G-proteins)

RN 170729-12-1 HCAPLUS

CN Acetamide, N-[2-(2,3,7,8-tetrahydro-1H-furo[2,3-g]indol-1-yl)ethyl]- (9CI)
(CA INDEX NAME)



REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 29 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1998:651749 HCAPLUS

DOCUMENT NUMBER: 130:20198

TITLE: Pharmacophoric search and 3D-QSAR comparative molecular field analysis studies on agonists of melatonin sheep receptors

AUTHOR(S): Marot, Christophe; Chavatte, Philippe; Morin-Allory, Luc; Viaud, Marie Claude; Guillaumet, Gerald; Renard, Pierre; Lesieur, Daniel; Michel, Andre

CORPORATE SOURCE: Institut de Chimie Organique et Analytique, Universite d'Orleans, Orleans, 45067, Fr.

SOURCE: Journal of Medicinal Chemistry (1998), 41(23), 4453-4465

CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Conformational anal. was used to characterize the agonist pharmacophore for melatonin sheep brain receptor recognition and activation. The mol. geometry shared by all conformations of the selected active ligands was

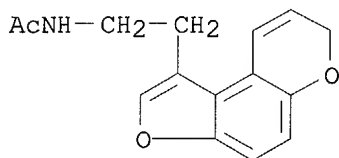
determined Assuming that all the compds. interact at the same binding site at the receptor level, 2-iodomelatonin pharmacophoric conformation served as a template for the superimposition of 64 structurally heterogeneous agonists constituting the training set used to perform a three-dimensional quant. structure-activity relationship study via the comparative mol. field anal. method. A statistically significant model was obtained for the totality of the compds. ($n = 64$, $q^2 = 0.62$, $N = 6$, $r^2 = 0.96$, $s = 0.28$, $F = 249$) with steric, electrostatic, and lipophilic relative contributions of 28%, 35%, and 37%, resp. The predictive power of the proposed model was discerned by successfully testing the 78 agonist ligands constituting the test set. The model so obtained and validated brings important structural insights to aid the design of novel melatoninergic agonist ligands prior to their synthesis.

IT 216391-25-2 216391-26-3

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(pharmacophoric search and 3D-QSAR comparative mol. field anal. studies on agonists of melatonin sheep receptors)

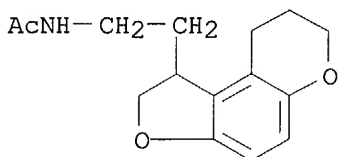
RN 216391-25-2 HCAPLUS

CN Acetamide, N-[2-(7H-furo[3,2-f][1]benzopyran-1-yl)ethyl]- (9CI) (CA INDEX NAME)



RN 216391-26-3 HCAPLUS

CN Acetamide, N-[2-(1,7,8,9-tetrahydro-2H-furo[3,2-f][1]benzopyran-1-yl)ethyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 30 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1998:618804 HCAPLUS

DOCUMENT NUMBER: 129:230717

TITLE: Polycyclic ethyl alkylamide melatonergic agents

INVENTOR(S): Epperson, James; Johnson, Graham; Keavy, Daniel J.; Takaki, Katherine S.

PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA

SOURCE: PCT Int. Appl., 31 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

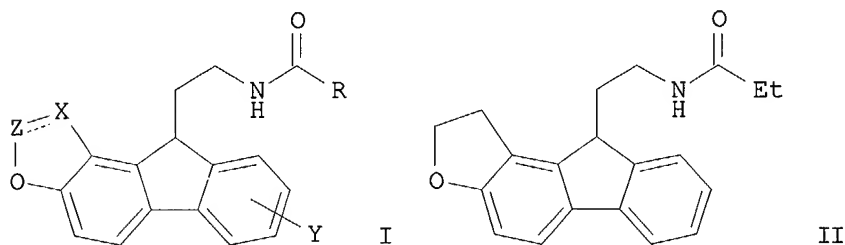
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

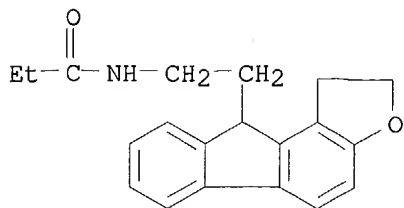
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------|------|-------|-----------------|-------|
| ----- | ---- | ----- | ----- | ----- |

| | | | | |
|------------------------|--|----------|----------------|------------|
| WO 9838991 | A1 | 19980911 | WO 1998-US4138 | 19980304 |
| W: | AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | |
| RW: | GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | |
| AU 9865405 | A1 | 19980922 | AU 1998-65405 | 19980304 |
| US 5948817 | A | 19990907 | US 1998-34912 | 19980304 |
| PRIORITY APPLN. INFO.: | | | US 1997-39885P | P 19970305 |
| | | | WO 1998-US4138 | W 19980304 |
| OTHER SOURCE(S): | MARPAT 129:230717 | | | |
| GI | | | | |

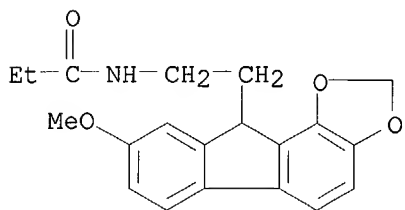


AB Novel polycyclic Et alkylamides I [Z = CH or (CH₂)₁₋₄; X = O, CH₂, CH; R = C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₁₋₃ haloalkyl, C₂₋₆ alkenyl, C₂₋₄ alkoxyalkyl, C₁₋₄ trifluoromethylalkyl, C₁₋₆ aminoalkyl; Y = H, C₁₋₆ alkoxy, halo] are useful as central nervous system agents. In particular, I are melatonin agonists, useful for treating sleep disorders and circadian rhythm disorders. For instance, title compound II was prepared in 10 steps: (1) Pd(0)-catalyzed coupling of 4-bromo-3-nitroanisole with phenylboronic acid (44%); (2) hydrogenation of the resultant 4-methoxy-2-nitro-1,1'-biphenyl to give the amine (100%); (3) amidation with pivaloyl chloride (93%); (4) lithiation and hydroxyethylation at the biphenyl 3-position (52%); (5) cyclization in 48% HBr to give a dihydrobenzofuran derivative (21%); (6) diazotization of the amino group and conversion to an iodide (57%); (7) lithiation and carboxylation with CO₂ (67%); (8) chlorination of the acid and further cyclization to give 2,10-dihydro-1H-fluoreno[2,1-b]furan-10-one; (9) Wittig-type reaction of the ketone with di-Et cyanomethylphosphonate; and (10) hydrogenation of the resultant nitrile in the presence of (EtCO)₂O. II bound to cloned ML1A melatonin receptors in vitro with IC₅₀ < 25 nM.

IT 212897-51-3P 212897-52-4P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of polycyclic Et alkylamides as melatonergic agents)
RN 212897-51-3 HCAPLUS
CN Propanamide, N-[2-(1,10-dihydro-2H-fluoreno[2,1-b]furan-10-yl)ethyl]-(9CI) (CA INDEX NAME)



RN 212897-52-4 HCAPLUS
 CN Propanamide, N-[2-(8-methoxy-10H-fluoreno[1,2-d]-1,3-dioxol-10-yl)ethyl]-
 (9CI) (CA INDEX NAME)



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 31 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1998:394595 HCAPLUS

DOCUMENT NUMBER: 129:117807

TITLE: GR196429: a nonindolic agonist at high-affinity
 melatonin receptors

AUTHOR(S): Beresford, Isabel J. M.; Browning, Christopher;
 Starkey, Sarah J.; Brown, Jason; Foord, Steven M.;
 Coughlan, Josephine; North, Peter C.; Dubocovich,
 Margarita L.; Hagan, Russell M.

CORPORATE SOURCE: Medicines Research Centre, Glaxo Wellcome Research and
 Development, Ltd., Hertfordshire, UK

SOURCE: Journal of Pharmacology and Experimental Therapeutics
 (1998), 285(3), 1239-1245
 CODEN: JPETAB; ISSN: 0022-3565

PUBLISHER: Williams & Wilkins

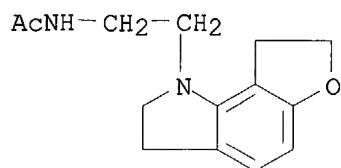
DOCUMENT TYPE: Journal

LANGUAGE: English

AB N-[2-[2,3,7,8-tetrahydro-1H-furo(2,3-g)indol-1-yl]ethyl]acetamide
 (GR196429) is a novel, nonindolic melatonin receptor agonist. GR196429
 had high affinity for human mt1 (pKi 9.9) and MT2 (pKi 9.8) receptors
 expressed in Chinese hamster ovary cells and for 2-[125I]-iodomelatonin
 binding sites in human cerebellum, guinea pig superior colliculus and
 hypothalamus and chicken retina and tectum (pKi 8.8-9.5). GR196429 was
 inactive at a wide range of other hormone and neurotransmitter receptors.
 In Chinese hamster ovary cells expressing human mt1 or MT2 receptors, both
 melatonin and GR196429 dose-dependently inhibited forskolin-stimulated
 cAMP accumulation. In rabbit isolated retina, GR196429 inhibited
 calcium-dependent [3H]-dopamine release with potency (IC50 30 pM) and maximum
 effect (76±5% at 1 nM) similar to those of melatonin. The response was
 antagonized by the melatonin receptor antagonist luzindole (1 µM). In
 slices of rat brain suprachiasmatic nucleus, perfusion (1 h) with GR196429
 at zeitgeber time 10 phase advanced the circadian peak in neuronal
 activity measured on the following day, with a maximum phase advance of
 2.7±0.3 h at 10 pM and an EC50 of 0.6 pM, results that indicated a

melatonin-like action on the phase of the circadian clock. CNS penetration and duration of receptor occupancy was determined in an ex vivo radioligand binding assay. In membranes of guinea pig superior colliculus prepared 30 min after administration of GR196429 (s.c.), 2-[125I]-iodomelatonin binding was inhibited with an ED50 of 0.04 mg/kg. After a dose of 1 mg/kg, binding was significantly inhibited for at least 3 h. Thus GR196429 is a potent and selective agonist at high-affinity melatonin receptors, which modulates circadian rhythms in an in vitro model of the circadian clock and which readily penetrates the CNS.

IT 170729-12-1, GR196429
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
 (GR196429 as a nonindolic agonist at high-affinity melatonin receptors)
 RN 170729-12-1 HCAPLUS
 CN Acetamide, N-[2-(2,3,7,8-tetrahydro-1H-furo[2,3-g]indol-1-yl)ethyl]- (9CI)
 (CA INDEX NAME)



REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 32 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1997:618091 HCAPLUS

DOCUMENT NUMBER: 127:278142

TITLE: Preparation of tricyclic compounds with binding affinity for melatonin receptor

INVENTOR(S): Ohkawa, Shigenori; Uchikawa, Osamu; Fukatsu, Kohji; Miyamoto, Masaomi

PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan

SOURCE: PCT Int. Appl., 269 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

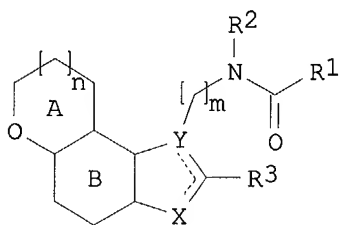
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------|--|----------|-----------------|----------|
| WO 9732871 | A1 | 19970912 | WO 1997-JP677 | 19970305 |
| W: | AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, GH, HU, IL, IS, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | |
| RW: | GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | |
| CA 2241666 | AA | 19970912 | CA 1997-2241666 | 19970305 |
| AU 9722318 | A1 | 19970922 | AU 1997-22318 | 19970305 |
| AU 706610 | B2 | 19990617 | | |
| EP 885210 | A1 | 19981223 | EP 1997-905450 | 19970305 |
| EP 885210 | B1 | 20020612 | | |
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| CN 1212691 | A | 19990331 | CN 1997-192700 | 19970305 |
| EP 1199304 | A1 | 20020424 | EP 2001-119552 | 19970305 |

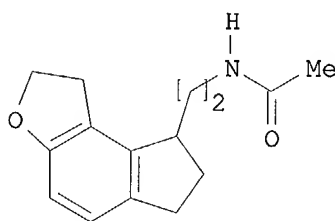
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, FI

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| AT 219071 | E | 20020615 | AT 1997-905450 | 19970305 |
| PT 885210 | T | 20020930 | PT 1997-905450 | 19970305 |
| ES 2175350 | T3 | 20021116 | ES 1997-905450 | 19970305 |
| CZ 291626 | B6 | 20030416 | CZ 1998-2775 | 19970305 |
| SK 283970 | B6 | 20040608 | SK 1998-1150 | 19970305 |
| US 6034239 | A | 20000307 | US 1997-812168 | 19970306 |
| TW 562803 | B | 20031121 | TW 1997-86102717 | 19970306 |
| JP 10287665 | A2 | 19981027 | JP 1997-52175 | 19970307 |
| JP 2884153 | B2 | 19990419 | | |
| JP 11152281 | A2 | 19990608 | JP 1998-268110 | 19970307 |
| NO 9803970 | A | 19980828 | NO 1998-3970 | 19980828 |
| US 6218429 | B1 | 20010417 | US 1999-309519 | 19990510 |
| PRIORITY APPLN. INFO.: | | | JP 1996-51491 | A 19960308 |
| | | | JP 1996-183667 | A 19960712 |
| | | | JP 1997-29185 | A 19970213 |
| | | | US 1996-13733P | P 19960320 |
| | | | US 1996-23090P | P 19960725 |
| | | | EP 1997-905450 | A3 19970305 |
| | | | WO 1997-JP677 | W 19970305 |
| | | | US 1997-812168 | A3 19970306 |
| | | | JP 1997-52175 | A3 19970307 |

OTHER SOURCE(S): MARPAT 127:278142
GI



I



II

AB The title compds. [I; R1 = (un)substituted alkyl, NH2, heterocyclyl; R2 = H, (un)substituted alkyl; R3 = H, (un)substituted alkyl, heterocyclyl; X = CHR4, NR4, O, S (wherein R4 = H, alkyl); Y = C, CH, N (when X = CH2, Y = C, CH); ring A = (un)substituted 5-7 membered O-containing heterocyclyl; ring B = (un)substituted benzene ring; m = 1-4; n = 0-2], useful as regulating agent of circadian rhythm, sleep-awake rhythm and time zone change syndrome, and for the treatment of sleep disorders, were prepared and formulated. Thus, treatment of 2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethylamine.HBr with Ac2O and 1N NaOH in THF afforded 66% II which showed IC50 of 0.28 nM against 2-[125I]iodomelatonin binding.

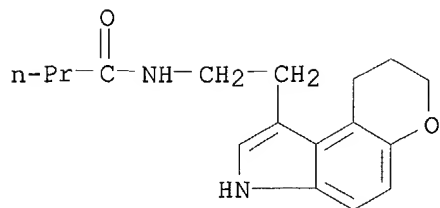
IT 196597-20-3P 196597-24-7P 196597-46-3P
196597-53-2P 196597-56-5P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

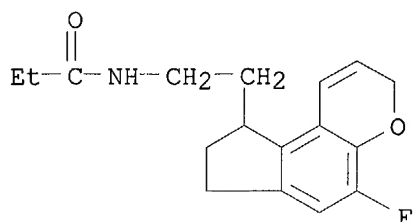
(preparation of tricyclic compds. with binding affinity for melatonin receptor)

RN 196597-20-3 HCAPLUS

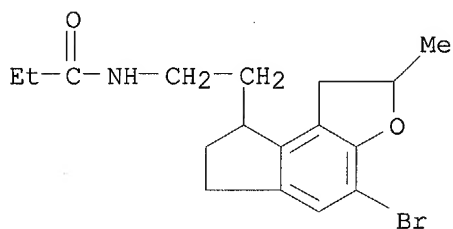
CN Butanamide, N-[2-(3,7,8,9-tetrahydropyrano[3,2-e]indol-1-yl)ethyl]- (9CI)
(CA INDEX NAME)



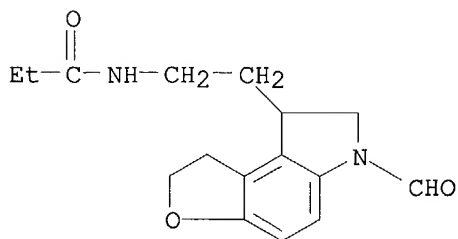
RN 196597-24-7 HCAPLUS
 CN Propanamide, N-[2-(5-fluoro-3,7,8,9-tetrahydrocyclopenta[f][1]benzopyran-9-yl)ethyl]- (9CI) (CA INDEX NAME)



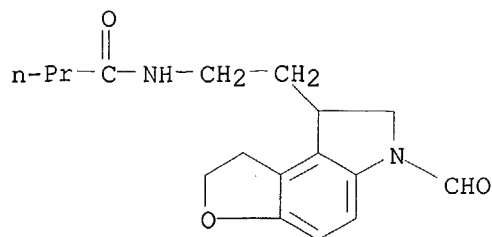
RN 196597-46-3 HCAPLUS
 CN Propanamide, N-[2-(4-bromo-1,6,7,8-tetrahydro-2-methyl-2H-indeno[5,4-b]furan-8-yl)ethyl]- (9CI) (CA INDEX NAME)



RN 196597-53-2 HCAPLUS
 CN Propanamide, N-[2-(6-formyl-1,6,7,8-tetrahydro-2H-furo[3,2-e]indol-8-yl)ethyl]- (9CI) (CA INDEX NAME)



RN 196597-56-5 HCAPLUS
 CN Butanamide, N-[2-(6-formyl-1,6,7,8-tetrahydro-2H-furo[3,2-e]indol-8-yl)ethyl]- (9CI) (CA INDEX NAME)

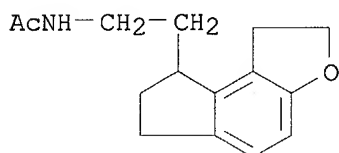


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 196597-59-8P 196597-60-1P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (preparation of tricyclic compds. with binding affinity for melatonin receptor)

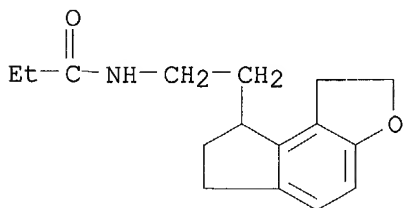
RN 196597-16-7 HCAPLUS

CN Acetamide, N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]-
 (9CI) (CA INDEX NAME)



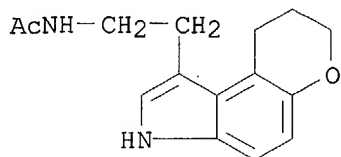
RN 196597-17-8 HCAPLUS

CN Propanamide, N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]-
 (9CI) (CA INDEX NAME)

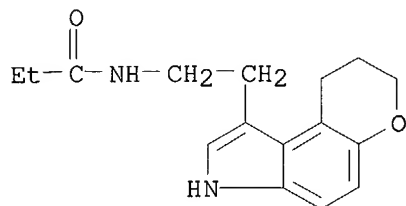


RN 196597-18-9 HCAPLUS

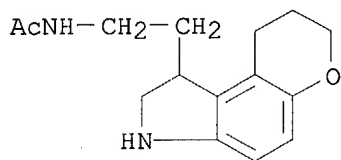
CN Acetamide, N-[2-(3,7,8,9-tetrahydropyrano[3,2-e]indol-1-yl)ethyl]- (9CI)
 (CA INDEX NAME)



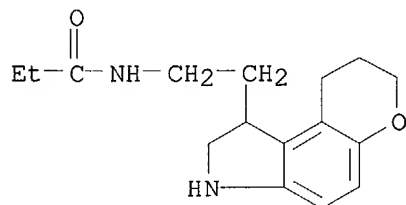
RN 196597-19-0 HCAPLUS
 CN Propanamide, N-[2-(3,7,8,9-tetrahydropyrano[3,2-e]indol-1-yl)ethyl]- (9CI)
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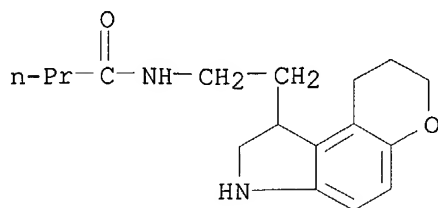
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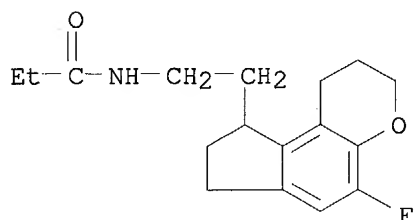
RN 196597-22-5 HCAPLUS
 CN Propanamide, N-[2-(1,2,3,7,8,9-hexahydropyrano[3,2-e]indol-1-yl)ethyl]- (9CI) (CA INDEX NAME)



RN 196597-23-6 HCAPLUS
 CN Butanamide, N-[2-(1,2,3,7,8,9-hexahydropyrano[3,2-e]indol-1-yl)ethyl]- (9CI) (CA INDEX NAME)

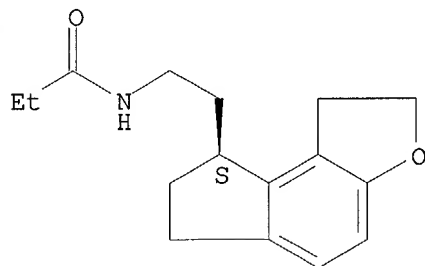


RN 196597-25-8 HCAPLUS
 CN Propanamide, N-[2-(5-fluoro-1,2,3,7,8,9-hexahydrocyclopenta[f][1]benzopyran-9-yl)ethyl]- (9CI) (CA INDEX NAME)



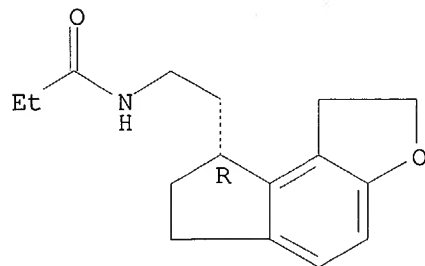
RN 196597-26-9 HCAPLUS
 CN Propanamide, N-[2-[(8S)-1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



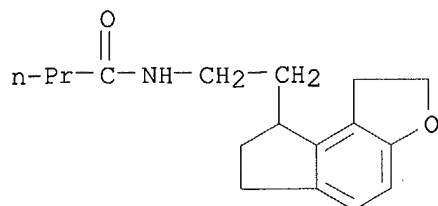
RN 196597-27-0 HCAPLUS
 CN Propanamide, N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



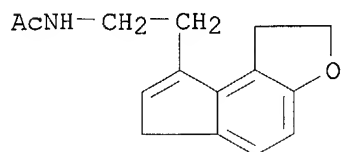
RN 196597-28-1 HCAPLUS

CN Butanamide, N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]-
(9CI) (CA INDEX NAME)



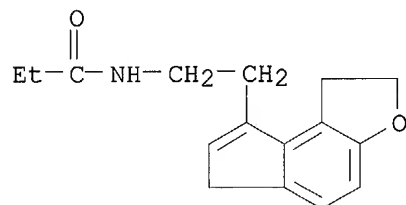
RN 196597-29-2 HCAPLUS

CN Acetamide, N-[2-(1,6-dihydro-2H-indeno[5,4-b]furan-8-yl)ethyl]- (9CI) (CA
INDEX NAME)



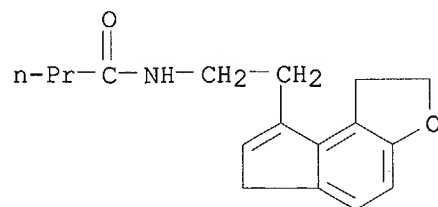
RN 196597-30-5 HCAPLUS

CN Propanamide, N-[2-(1,6-dihydro-2H-indeno[5,4-b]furan-8-yl)ethyl]- (9CI)
(CA INDEX NAME)



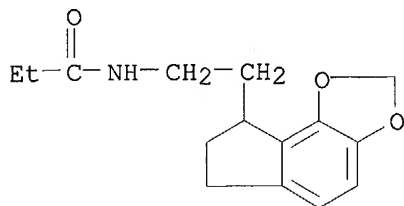
RN 196597-31-6 HCAPLUS

CN Butanamide, N-[2-(1,6-dihydro-2H-indeno[5,4-b]furan-8-yl)ethyl]- (9CI)
(CA INDEX NAME)

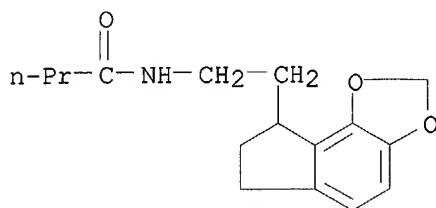


RN 196597-34-9 HCAPLUS

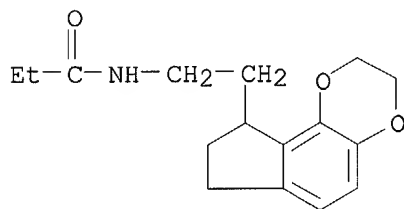
CN Propanamide, N-[2-(7,8-dihydro-6H-indeno[4,5-d]-1,3-dioxol-8-yl)ethyl]-
(9CI) (CA INDEX NAME)



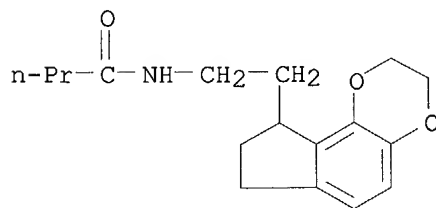
RN 196597-35-0 HCAPLUS
 CN Butanamide, N-[2-(7,8-dihydro-6H-indeno[4,5-d]-1,3-dioxol-8-yl)ethyl]-
 (9CI) (CA INDEX NAME)



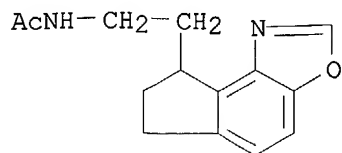
RN 196597-36-1 HCAPLUS
 CN Propanamide, N-[2-(2,3,8,9-tetrahydro-7H-indeno[4,5-b]-1,4-dioxin-9-yl)ethyl]- (9CI) (CA INDEX NAME)



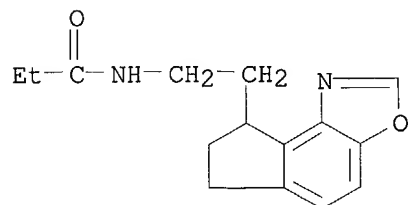
RN 196597-37-2 HCAPLUS
 CN Butanamide, N-[2-(2,3,8,9-tetrahydro-7H-indeno[4,5-b]-1,4-dioxin-9-yl)ethyl]- (9CI) (CA INDEX NAME)



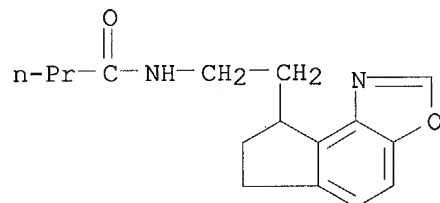
RN 196597-38-3 HCAPLUS
 CN Acetamide, N-[2-(7,8-dihydro-6H-indeno[4,5-d]oxazol-8-yl)ethyl]- (9CI)
 (CA INDEX NAME)



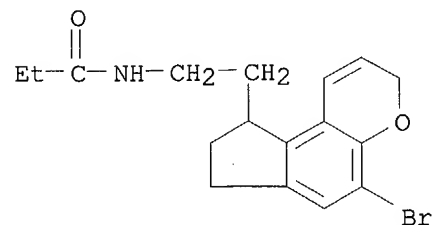
RN 196597-39-4 HCAPLUS
 CN Propanamide, N-[2-(7,8-dihydro-6H-indeno[4,5-d]oxazol-8-yl)ethyl]- (9CI)
 (CA INDEX NAME)



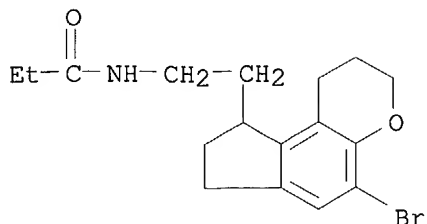
RN 196597-40-7 HCAPLUS
 CN Butanamide, N-[2-(7,8-dihydro-6H-indeno[4,5-d]oxazol-8-yl)ethyl]- (9CI)
 (CA INDEX NAME)



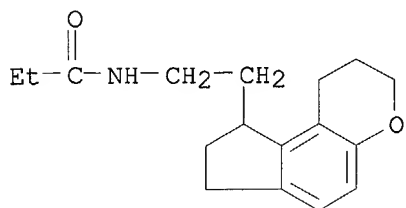
RN 196597-41-8 HCAPLUS
 CN Propanamide, N-[2-(5-bromo-3,7,8,9-tetrahydrocyclopenta[f][1]benzopyran-9-yl)ethyl]- (9CI) (CA INDEX NAME)



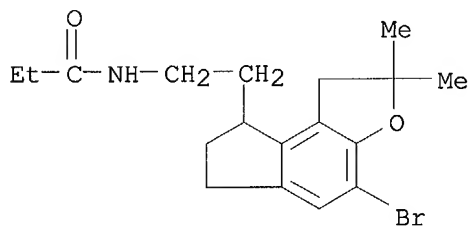
RN 196597-42-9 HCAPLUS
 CN Propanamide, N-[2-(5-bromo-1,2,3,7,8,9-hexahydrocyclopenta[f][1]benzopyran-9-yl)ethyl]- (9CI) (CA INDEX NAME)



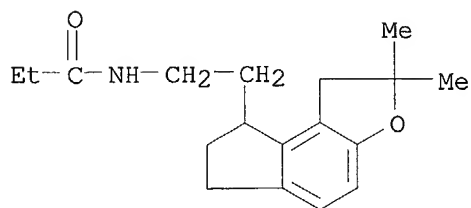
RN 196597-43-0 HCAPLUS
 CN Propanamide, N-[2-(1,2,3,7,8,9-hexahydrocyclopenta[f][1]benzopyran-9-yl)ethyl]- (9CI) (CA INDEX NAME)



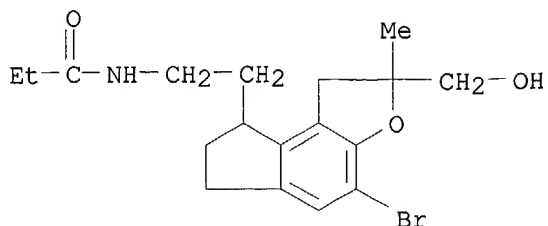
RN 196597-44-1 HCAPLUS
 CN Propanamide, N-[2-(4-bromo-1,6,7,8-tetrahydro-2,2-dimethyl-2H-indeno[5,4-b]furan-8-yl)ethyl]- (9CI) (CA INDEX NAME)



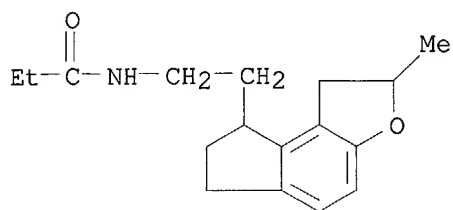
RN 196597-45-2 HCAPLUS
 CN Propanamide, N-[2-(1,6,7,8-tetrahydro-2,2-dimethyl-2H-indeno[5,4-b]furan-8-yl)ethyl]- (9CI) (CA INDEX NAME)



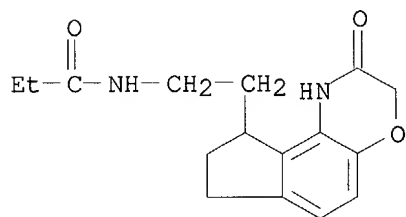
RN 196597-47-4 HCAPLUS
 CN Propanamide, N-[2-[4-bromo-1,6,7,8-tetrahydro-2-(hydroxymethyl)-2-methyl-2H-indeno[5,4-b]furan-8-yl]ethyl]- (9CI) (CA INDEX NAME)



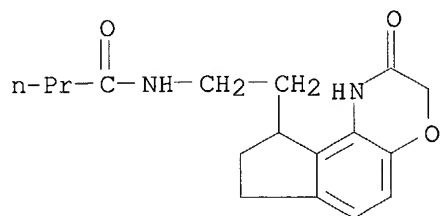
RN 196597-48-5 HCAPLUS
 CN Propanamide, N-[2-(1,6,7,8-tetrahydro-2-methyl-2H-indeno[5,4-b]furan-8-yl)ethyl]- (9CI) (CA INDEX NAME)



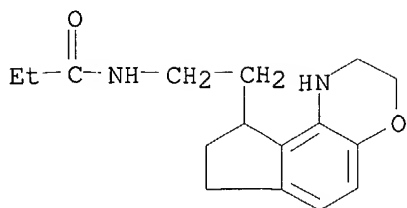
RN 196597-49-6 HCAPLUS
 CN Propanamide, N-[2-(1,2,3,7,8,9-hexahydro-2-oxoindeno[5,4-b][1,4]oxazin-9-yl)ethyl]- (9CI) (CA INDEX NAME)



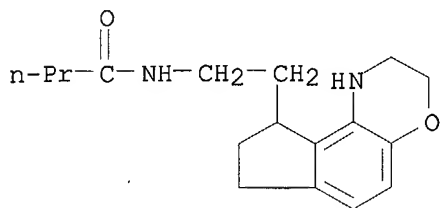
RN 196597-50-9 HCAPLUS
 CN Butanamide, N-[2-(1,2,3,7,8,9-hexahydro-2-oxoindeno[5,4-b][1,4]oxazin-9-yl)ethyl]- (9CI) (CA INDEX NAME)



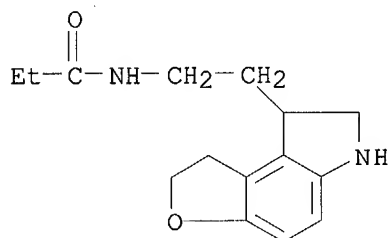
RN 196597-51-0 HCAPLUS
 CN Propanamide, N-[2-(1,2,3,7,8,9-hexahydroindeno[5,4-b][1,4]oxazin-9-yl)ethyl]- (9CI) (CA INDEX NAME)



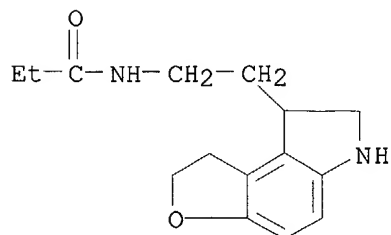
RN 196597-52-1 HCAPLUS
 CN Butanamide, N-[2-(1,2,3,7,8,9-hexahydroindeno[5,4-b][1,4]oxazin-9-yl)ethyl]- (9CI) (CA INDEX NAME)



RN 196597-54-3 HCAPLUS
 CN Propanamide, N-[2-(1,6,7,8-tetrahydro-2H-furo[3,2-e]indol-8-yl)ethyl]- (9CI) (CA INDEX NAME)



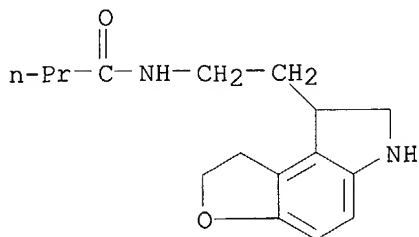
RN 196597-55-4 HCAPLUS
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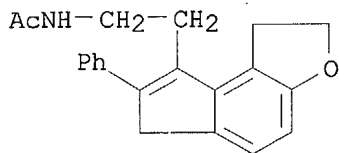
● HCl

RN 196597-57-6 HCAPLUS

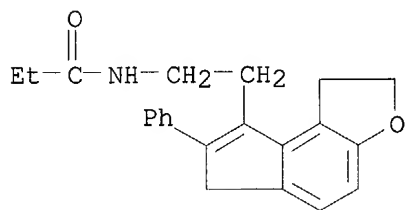
CN Butanamide, N-[2-(1,6,7,8-tetrahydro-2H-furo[3,2-e]indol-8-yl)ethyl]-
(9CI) (CA INDEX NAME)



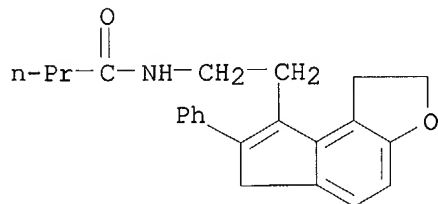
RN 196597-58-7 HCAPLUS
CN Acetamide, N-[2-(1,6-dihydro-7-phenyl-2H-indeno[5,4-b]furan-8-yl)ethyl]-
(9CI) (CA INDEX NAME)



RN 196597-59-8 HCAPLUS
CN Propanamide, N-[2-(1,6-dihydro-7-phenyl-2H-indeno[5,4-b]furan-8-yl)ethyl]-
(9CI) (CA INDEX NAME)



RN 196597-60-1 HCAPLUS
CN Butanamide, N-[2-(1,6-dihydro-7-phenyl-2H-indeno[5,4-b]furan-8-yl)ethyl]-
(9CI) (CA INDEX NAME)



L29 ANSWER 33 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:220137 HCAPLUS
DOCUMENT NUMBER: 127:1057
TITLE: Melatonin receptor antagonists that differentiate

between the human Mella and Mellb recombinant subtypes are used to assess the pharmacological profile of the rabbit retina ML1 presynaptic heteroreceptor

AUTHOR(S): Dubocovich, Margarita L.; Masana, Monica I.; Iacob, Stanca; Sauri, Daniel M.

CORPORATE SOURCE: Med. Sch., Northwestern University Chicago, Chicago, IL, 60611, USA

SOURCE: Naunyn-Schmiedeberg's Archives of Pharmacology (1997), 355(3), 365-375

CODEN: NSAPCC; ISSN: 0028-1298

PUBLISHER: Springer

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Subtype-selective agonists, partial agonists, and antagonists which distinguish the human recombinant Mella and Mellb melatonin receptors expressed in COS-7 cells were identified. Melatonin receptor agonists showed higher affinity for competition of 2-[125I]-iodomelatonin binding for the Mellb than the Mella melatonin receptor. The dissociation consts. (Ki) of 16 agonists determined on the recombinant human Mella and Mellb melatonin receptor subtypes showed a correlation. Six agonists showed 10-60-fold higher affinity for the Mellb melatonin receptor as indicated by the affinity selectivity ratios (Mella/Mellb). Dissociation consts. for competition of 11 partial agonists and antagonists for 2-[125I]-iodomelatonin binding were 15.5-362-fold higher for the Mellb than for the Mella melatonin receptor. The lack of correlation between the pKi values strongly suggest that the 2 human melatonin receptor subtypes can be distinguished pharmacol. The partial agonist 5-methoxyluzindole and the competitive melatonin receptor antagonists GR128107, 4-phenyl-2-chloroacetamidotetraline, 4-phenyl-2-acetamidotetraline, and 4-phenyl-2-propionamidotetraline are selective Mellb melatonin receptor analogs as their affinity selectivity ratios (Mella/Mellb) are >100. It is concluded that the 40% overall amino acid difference in the sequence of the human recombinant Mella and Mellb melatonin receptors is reflected in distinct pharmacol. profiles for the subtypes. The pharmacol. profile of the presynaptic ML1 melatonin heteroreceptor of rabbit retina mediating inhibition of the Ca-dependent release of dopamine was compared to that of the recombinant Mella and Mellb melatonin receptors. Melatonin inhibited [3H]dopamine release by 50% (IC50) at 20 pM with a maximal inhibitory effect (80%) at 1 nM. The partial agonists showed various degrees of efficacy while none of the competitive melatonin receptor antagonists did inhibit [3H]dopamine release on their own. The potency (IC50) of full melatonin receptor agonists correlated with their affinity to compete for 2-[125I]-iodomelatonin binding to either the Mella or Mellb human melatonin receptors. The apparent dissociation consts. (KB) for partial agonists and antagonists to antagonize the inhibition of [3H]dopamine release mediated by activation of the ML1 heteroreceptor by melatonin, correlated with the affinity consts. (Ki) for 2-[125I]-iodomelatonin binding determined on the Mellb but not the Mella subtype. These results demonstrate that the pharmacol. profile of the human recombinant Mellb melatonin receptor is similar to that of the functional presynaptic melatonin heteroreceptor of rabbit retina, which is referred as an ML1 subtype. It is concluded that the selective Mellb melatonin partial agonists and antagonists described here can be used to identify melatonin receptor subtypes in native tissues and to search for subtype selective analogs with therapeutic potential.

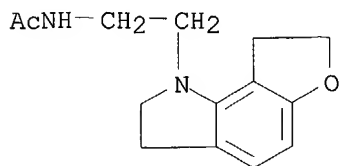
IT 170729-12-1, GR 196429

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(pharmacol. profile of rabbit retina ML1 presynaptic heteroreceptor by melatonin receptor antagonists distinguishing human recombinant Mella and Mellb subtypes)

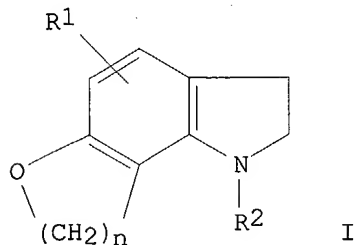
RN 170729-12-1 HCAPLUS

CN Acetamide, N-[2-(2,3,7,8-tetrahydro-1H-furo[2,3-g]indol-1-yl)ethyl]- (9CI)
(CA INDEX NAME)



L29 ANSWER 34 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:943453 HCAPLUS
DOCUMENT NUMBER: 123:340087
TITLE: Preparation of indolines which are melatonin receptor agonists and antagonists
INVENTOR(S): North, Peter Charles; Carter, Malcolm Clive
PATENT ASSIGNEE(S): Glaxo Group Ltd., UK
SOURCE: PCT Int. Appl., 42 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|-------------------|-----------------|----------|
| WO 9517405 | A1 | 19950629 | WO 1994-EP4220 | 19941220 |
| W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN | | | | |
| RW: KE, MW, SD, SZ, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| ZA 9410056 | A | 19951018 | ZA 1994-10056 | 19941219 |
| CA 2179402 | AA | 19950629 | CA 1994-2179402 | 19941220 |
| AU 9512743 | A1 | 19950710 | AU 1995-12743 | 19941220 |
| AU 684877 | B2 | 19980108 | | |
| EP 736028 | A1 | 19961009 | EP 1995-903817 | 19941220 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE | | | | |
| IL 112097 | A1 | 19980615 | IL 1994-112097 | 19941221 |
| US 5633276 | A | 19970527 | US 1996-652460 | 19960614 |
| PRIORITY APPLN. INFO.: | | | GB 1993-26192 | 19931222 |
| | | | WO 1994-EP4220 | 19941220 |
| OTHER SOURCE(S): | | MARPAT 123:340087 | | |
| GI | | | | |



AB The title compds. [I; R1 = H, halogen, C1-6 alkyl; R2 =

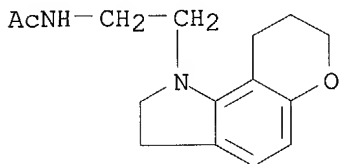
CR3R4(CH2)pNR5COR6; R3-R5 = H, C1-6 alkyl; R6 = C1-6 alkyl, C3-7 cycloalkyl; p = 1-4; n = 2-4], useful as melatonin receptor agonists and antagonists in the treatment of conditions associated with a disturbed functioning of the melatonin system [i.e., jet lag (no data), osteoporosis (no data), CNS disorders (no data), etc. (no data)], are prepared and I-containing formulations presented. Thus, 2-(5-chloro-2,3,7,8-tetrahydro-1H-furo[2,3-g]indol-1-yl)ethylamine was amidated with Ac2O, producing N-[2-(5-chloro-2,3,7,8-tetrahydro-1H-furo[2,3-g]indol-1-yl)ethyl]acetamide, m.p. 147-149°, which demonstrated a IC50 against the binding of melatonin to rabbit retina of 0.004 nM.

IT 170728-91-3P 170728-92-4P 170729-12-1P
170729-13-2P 170729-14-3P 170729-15-4P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of indolines which are melatonin receptor agonists and antagonists)

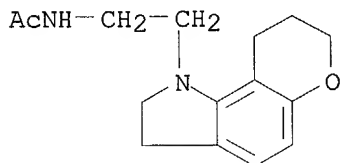
RN 170728-91-3 HCAPLUS

CN Acetamide, N-[2-(2,3,8,9-tetrahydropyrano[2,3-g]indol-1(7H)-yl)ethyl]-
(9CI) (CA INDEX NAME)



RN 170728-92-4 HCAPLUS

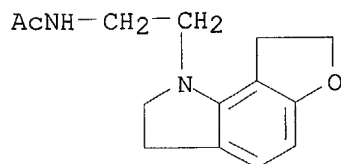
CN Acetamide, N-[2-(2,3,8,9-tetrahydropyrano[2,3-g]indol-1(7H)-yl)ethyl]-,
monohydrochloride (9CI) (CA INDEX NAME)



● HCl

RN 170729-12-1 HCAPLUS

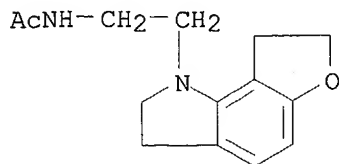
CN Acetamide, N-[2-(2,3,7,8-tetrahydro-1H-furo[2,3-g]indol-1-yl)ethyl]- (9CI)
(CA INDEX NAME)



RN 170729-13-2 HCAPLUS

CN Acetamide, N-[2-(2,3,7,8-tetrahydro-1H-furo[2,3-g]indol-1-yl)ethyl]-,

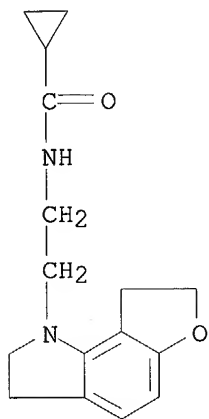
monohydrochloride (9CI) (CA INDEX NAME)



● HCl

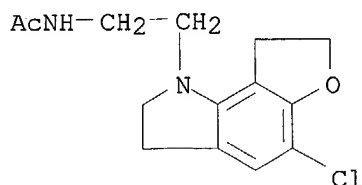
RN 170729-14-3 HCAPLUS

CN Cyclopropanecarboxamide, N-[2-(2,3,7,8-tetrahydro-1H-furo[2,3-g]indol-1-yl)ethyl]- (9CI) (CA INDEX NAME)



RN 170729-15-4 HCAPLUS

CN Acetamide, N-[2-(5-chloro-2,3,7,8-tetrahydro-1H-furo[2,3-g]indol-1-yl)ethyl]- (9CI) (CA INDEX NAME)



L29 ANSWER 35 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1995:827741 HCAPLUS

DOCUMENT NUMBER: 123:256419

TITLE: An unusual byproduct in a concise synthesis of a rotationally restricted phenolic analog of serotonin

AUTHOR(S): Macor, John E.

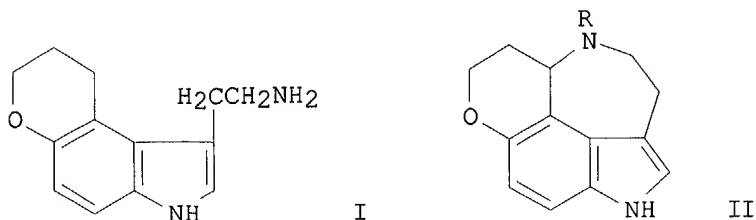
CORPORATE SOURCE: Fisons Pharm., Rochester, NY, 14603, USA

SOURCE: Tetrahedron Letters (1995), 36(39), 7019-22

CODEN: TELEAY; ISSN: 0040-4039

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal
 LANGUAGE: English
 OTHER SOURCE(S): CASREACT 123:256419
 GI



AB An improved synthesis of a dihydropyrano[3,-2e]indole analog I of serotonin has been accomplished. Starting with serotonin itself and utilizing a Claisen rearrangement/cyclization of a 5-propargyloxy-N-Cbz-tryptamine to form the pyrano[3,2-e]indole, the reaction sequence of four steps afforded a 36% overall yield of I. In the conversion, a unique tetracyclic byproduct II (R = Cbz, Me) was observed which arose from -NH- of the Cbz group adding across the olefin in the formed pyrano[3,2-e]indole. Conversion of II (R = Cbz) to the tertiary amine II (R = Me) added confirmation to the tetracyclic structure identification.

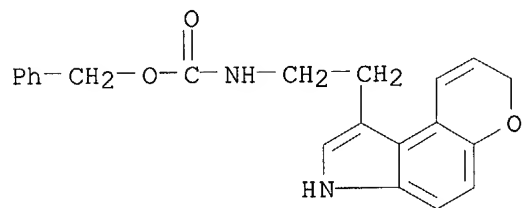
IT **169135-14-2P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(unusual byproduct in a concise synthesis of a rotationally restricted phenolic analog of serotonin)

RN 169135-14-2 HCAPLUS

CN Carbamic acid, [2-(3,7-dihydropyrano[3,2-e]indol-1-yl)ethyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)



L29 ANSWER 36 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1987:196345 HCAPLUS

DOCUMENT NUMBER: 106:196345

TITLE: Synthesis and pharmacological activity of 5,6- and 4,5-ethylendioxytryptamines

AUTHOR(S): Partsvaniya, D. A.; Akhvlediani, R. N.; Gordeev, E. N.; Vigdorchik, M. M.; Kuleshova, N. N.; Trubitsyna, T. K.; Mashkovskii, M. D.; Suvorov, N. N.

CORPORATE SOURCE: MKhTI im. Mendeleeva, Moscow, USSR

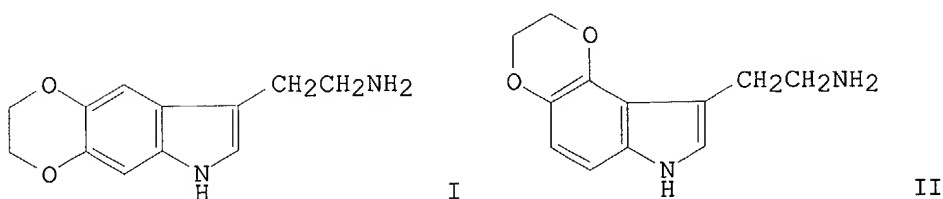
SOURCE: Khimiko-Farmatsevticheskii Zhurnal (1986), 20(12), 1454-9

CODEN: KHFZAN; ISSN: 0023-1134

DOCUMENT TYPE: Journal

LANGUAGE: Russian

GI



AB Japp-Klingemann reaction of the diazonium salt of 6-amino-1,4-benzodioxane with Et α -acetyl- δ -phthalimidovaleate gave 3,4-ethylenedioxyphenylhydrazone Et ester of α -keto- δ -phthalimidovaleic acid in 82% yield. This was then subjected to Fischer cyclization with a saturated alc. HCl solution to give the linear and angular isomers in a ratio of 6:1. Alkaline hydrolysis followed by thermal decarboxylation and N₂H₄ treatment gave I and II. The overall yield of I was 20% and of II 2%. The yield and purity of the compds. were higher than those from the Japp-Klingemann reaction of the benzodioxane with K 2-piperidone-3-carboxylate. II was close to mexamine in its pharmacol. activity and toxicity and showed strong sympathomimetic activity. In contrast, I was not very active.

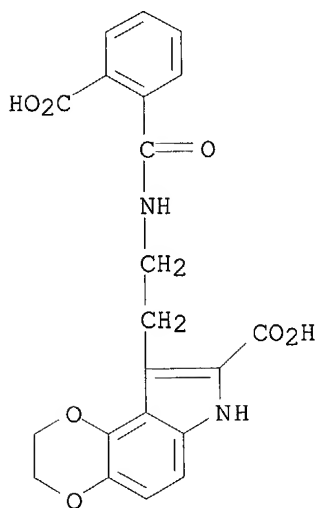
IT 108097-95-6P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation and thermal decarboxylation of)

RN 108097-95-6 HCAPLUS

CN 7H-1,4-Dioxino[2,3-e]indole-8-carboxylic acid, 9-[2-[(2-carboxybenzoyl)amino]ethyl]-2,3-dihydro- (9CI) (CA INDEX NAME)



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